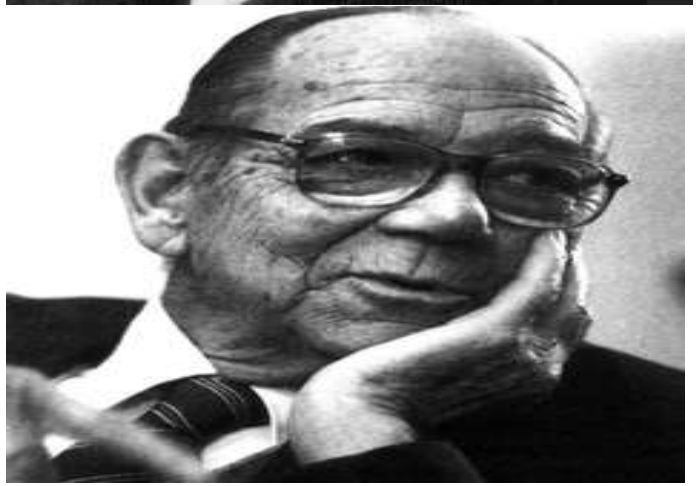
Novel Strategies For Anemia Treatment is there really anything new on the horizon?

By

Alaa Sabry.,MD

History

- in 1835 **Richard Bright:** first suggestion was made that the kidney might be involved in erythropoiesis .
- At the beginning of the twentieth century, **Paul Carnot and Deflandre** reported that serum from an anemic donor rabbit injected into a normal rabbit resulted in increased erythropoiesis. (Hemopoitien)
- In 1957, **Jacobson, Goldwasser** and others showed that the kidney was the source of this substance.
- Exactly 20 years later, **Miyake et** al isolated the hormone from urine of patients with aplastic anemia and named it EPO.



History

- Recombinant human erythropoietin was introduced as a treatment for the anemia associated with chronic kidney disease (CKD) in 1989 (in the United States) and 1990 (in Europe).
- The availability of recombinant human erythropoietin (rHuEPO) has revolutionized the management of anaemia in patients with CKD.
- It has transformed the lives of millions of patients:
  - Particularly those on dialysis therapy who were transfusion dependent,
  - Iron overloaded,
  - Severely debilitated from the symptoms associated with having an average hemoglobin level of 6-7 g/dL.

Currently Available Erythropoiesis-Stimulating Agents

Agent	Active Compound	Manufacturing Process	Year Licensed
Epoetin alfa/beta (Epogen, Eprex, Erypo, NeoRecormon)	Recombinant human EPO	Recombinant DNA technology; EPO cDNA/gene–transfected CHO cells	1989 (Epogen, in US); 1990 (Eprex/ Erypo/NeoRecormon, in Europe)
Epoetin delta (Dynepo)	Recombinant human EPO	Recombinant DNA technology; EPO cDNA/gene–transfected human cells	2006 (outside of US); product withdrawn by Shire in 2009
"Biosimilar" epoetins (Binocrit, Hexal, Retacrit, Silapo, Eporatio)	Recombinant human EPO	Recombinant DNA technology; EPO cDNA/gene–transfected CHO cells	2009 onward
Nonapproved or locally approved "copy" epoetins	Recombinant human EPO	Recombinant DNA technology; EPO cDNA/gene-transfected human cells	Available in many countries outside of US and Europe, eg, India, China, Thailand, Argentina, Brazil
Darbepoetin alfa (Aranesp)	Hyperglycosylated recombinant human EPO analogue	Recombinant DNA technology; mutated EPO cDNA–transfected CHO cells	2001 (both US and Europe)
C.E.R.A. (Mircera)	Pegylated recombinant human EPO analogue		2009 (outside of US only)

Abbreviations: EPO, erythropoietin; cDNA, complementary DNA; C.E.R.A., continuous erythropoietin receptor activator; CHO, Chinese hamster ovary; US, United States.

History

- Current EPO analogue therapies rely upon supraphysiologic levels of recombinant variants of EPO to induce erythropoiesis .

- Intravenous Or subcutaneous, Oral or nasal more convenient but the bioavailability is insufficient.
- Unstable at Room temperatures , required cold chain from the manufacturing step till administration .
- Inadequate handling increases the risk of immunization by the drug
- Use of greater doses in CKD patients is associated with worsening hypertension and increased risk for CV events (myocardial infarction, hospitalization for congestive heart failure and stroke) .

Szczech LA, al. Kidney Int 2008; 74: 791–798

Zhang Y, et al. Am J Kidney Dis 2004; 44: 866–876

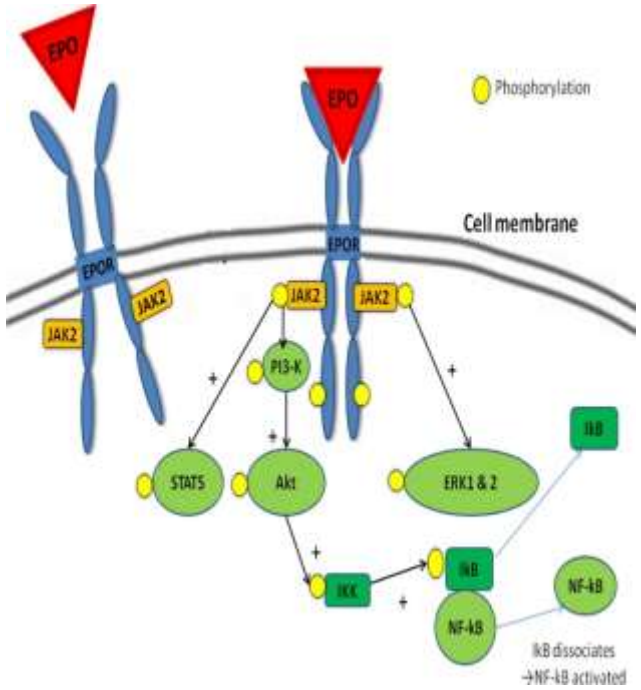
Future Erythropoiesis-Stimulating Agents

Agent	Active Compound	Manufacturing Process	Stage of Development
Peginesatide (Hematide)	Dimeric pegylated peptide	Synthetic peptide chemistry	Completed Phase 3
HIF stabilizers	Prolyl hydroxylase inhibitor	Chemical synthesis	Phase 1-2
Hepcidin modulation	Various	Various	Planning phase 1
GATA-2 inhibitors	Small molecule	Chemical synthesis	??
EPO gene therapy (EPODURE)	Skin cells (microdermis) transfected with the *EPO* gene	Biopump technology, harvesting skin biopsies and using adenovirus as vector	Phase 2

Abbreviations: EPO, erythropoietin; GATA-2, GATA-binding protein 2; HIF, hypoxia inducible factor.

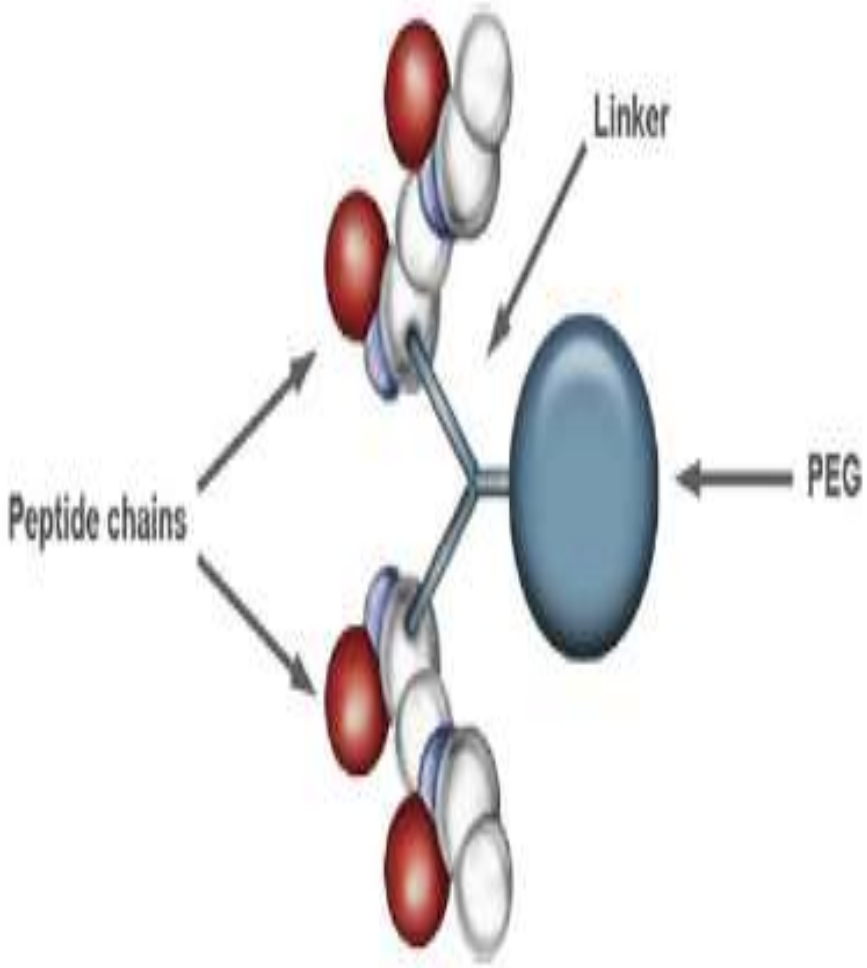
1- Erythropoietin Mimetic Peptides

Erythropoietin Mimetic Peptides
PEGINESATIDE



Peginesatide

- A novel EPO receptor agonist, is a synthetic, dimeric peptide linked to polyethylene glycol .
- This linkage enhances its metabolic stability in vivo by increasing EPO survival rates when in the presence of the EpoR receptor .
- No structural homology between peginesatide and erythropoietin, antibodies against erythropoietin do not crossreact with peginesatide.
- The manufacturing process for this peptide-based ESA involves much simpler techniques that are required for the manufacture of existing ESAs.



Peginesatide

- **Was approved by FDA in 2012.**
- **During clinical studies, its safety profile appeared to be safe, except the potential increase in the risk of safety end-point events in CKD patients not on dialyses.**
- **Unfortunately, soon after launch, unexpected toxicity including anaphylaxis, which can be life-threatening, or fatal, was identified.**
- **As a consequence Affymax, Inc. and Takeda Pharmaceutical Co. Ltd., along with the US FDA are informing the public of a voluntary recall of the entire lot of peginesatide injections in the user level .**

Locatelli F, Del Vecchio L. Expert Opin Pharmacother 2013 ;1277:8-14.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Peginesatide for Anemia in Patients with Chronic Kidney Disease Not Receiving Dialysis

Iain C. Macdougall, M.D., Robert Provenzano, M.D., Amit Sharma, M.D., Bruce S. Spinowitz, M.D., Rebecca J. Schmidt, D.O., Pablo E. Pergola, M.D., Ph.D., Raja I. Zabaneh, M.D., Sandra Tong-Starksen, M.D., Martha R. Mayo, Pharm.D., Hong Tang, M.S., Krishna R. Polu, M.D., Anne-Marie Duliege, M.D., and Steven Fishbane, M.D., for the PEARL Study Groups*

PEARL (Peginesatide for the Correction of Anemia in Patients with Chronic Renal Failure Not on Dialysis and Not Receiving Treatment with Erythropoiesis-Stimulating Agents)

N Engl J Med 2013;368:320-32.
DOI: 10.1056/NEJMoa1203166

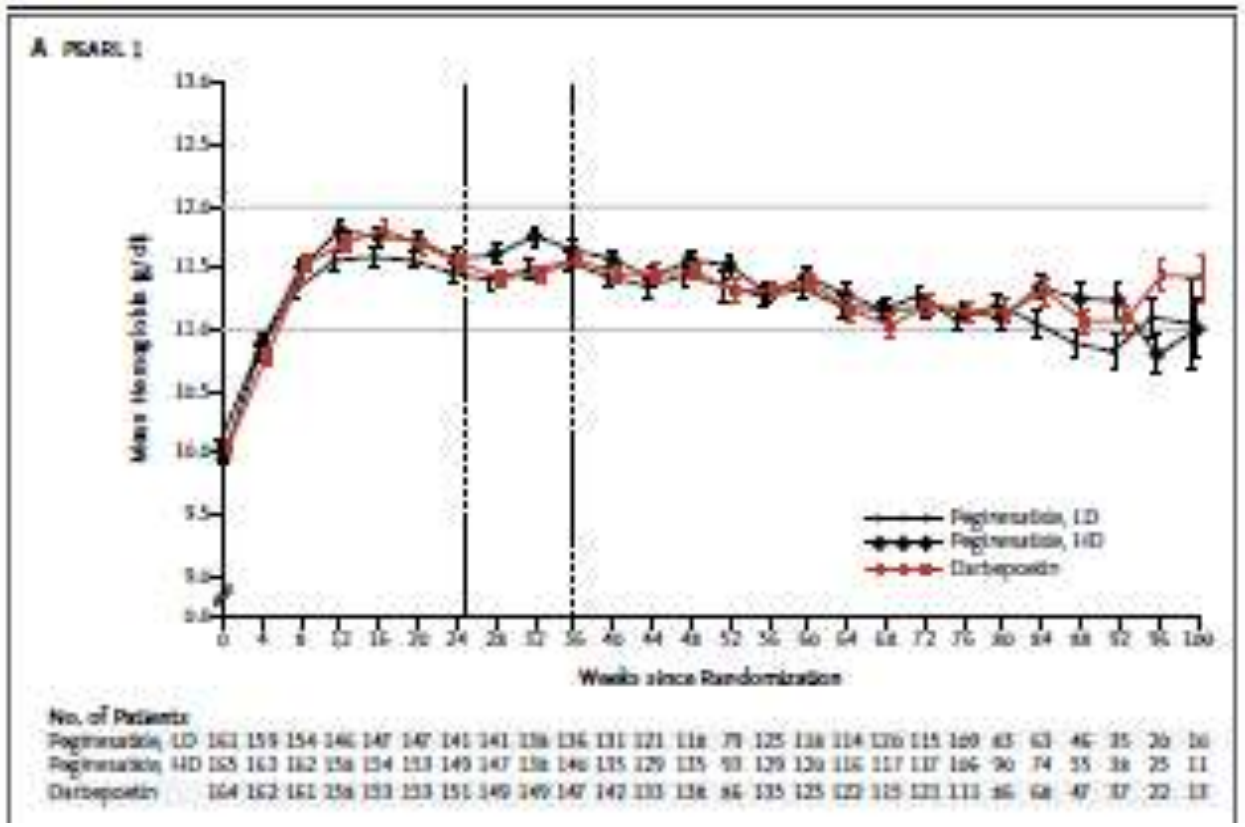
PEARL Studies

- Two similarly designed, phase 3, randomized, active-treatment–controlled, open label, noninferiority studies in the United States (PEARL 1 and 2) and in Europe (PEARL 2).
- Study Procedures:
- In PEARL 1, a total of 490 patients at 71 sites in the United States underwent randomization; in PEARL 2, a total of 493 patients at 43 sites in the United States and 19 sites in Europe underwent randomization.
- A period of 4 weeks for screening, 24 weeks for correction, 12 weeks for evaluation, and 16 weeks or more of additional follow-up.

Mean Hemoglobin Level According to Study Week.

The primary efficacy end point

Peginesatide was noninferior to darbepoetin in increasing and maintaining hemoglobin levels.



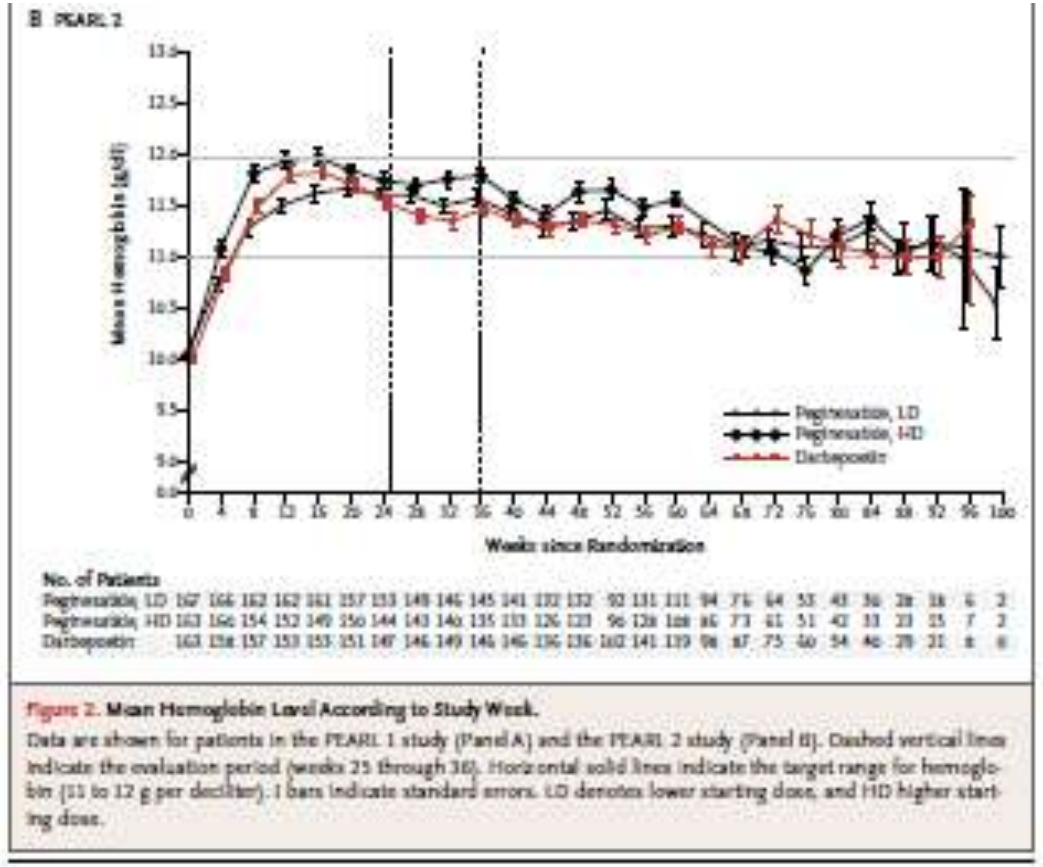


Figure 2. **Mean Hemoglobin Level According to Study Week.**

Data are shown for patients in the PEARL 1 study (Panel A) and the PEARL 2 study (Panel B). Dashed vertical lines indicate the evaluation period (weeks 25 through 36). Horizontal solid lines indicate the target range for hemoglobin (11 to 12 g per deciliter). I bars indicate standard errors. LD denotes lower starting dose, and HD higher starting dose.

PEARL Studies
Composite Safety End Point

- The hazard ratio for the cardiovascular safety end point was 1.32 (95% CI, 0.97 to 1.81) for peginesatide relative to darbepoetin.

- Numerically higher event rates in three categories:
- Death (8.8% vs. 6.7%),
- Unstable angina (2.4% vs. 0.9%).
- Arrhythmia (5.6% vs. 4.0%).

Table 2. Component Events of the Composite Safety End Point, Most Common Serious Adverse Events, and Adverse Events Associated with the Erythropoiesis-Stimulating-Agent (ESA) Class of Drugs.

Event	Peginesatide (N=656)	Darbepoetin (N=327)
	no. of patients (%)	
Component events of the composite safety end point*		
Death	58 (8.8)	22 (6.7)
Cardiovascular	8 (1.2)	5 (1.5)
Noncardiovascular	20 (3.0)	12 (3.7)
Sudden†	14 (2.1)	1 (0.3)
Unknown cause‡	16 (2.4)	4 (1.2)
Stroke	7 (1.1)	3 (0.9)
Myocardial infarction	24 (3.7)	11 (3.4)
Congestive heart failure	56 (8.5)	28 (8.6)
Unstable angina	16 (2.4)	3 (0.9)
Arrhythmia	37 (5.6)	13 (4.0)
Serious adverse events occurring in ≥3% of patients in either group§		
Congestive cardiac failure	56 (8.5)	26 (8.0)
Acute renal failure	56 (8.5)	14 (4.3)
Chronic renal failure	31 (4.7)	15 (4.6)
Pneumonia	33 (5.0)	14 (4.3)
Urinary tract infection	24 (3.7)	8 (2.4)
Anemia	23 (3.5)	5 (1.5)
Hypoglycemia	12 (1.8)	11 (3.4)
Adverse-event categories associated with the ESA class of drugs¶		
Hypertension-related events	126 (19.2)	65 (19.9)
Thromboembolic events		
Arterial	39 (5.9)	16 (4.9)
Venous	14 (2.1)	6 (1.8)
Complications related to vascular access	11 (1.7)	6 (1.8)
Convulsions	8 (1.2)	1 (0.3)
Infusion- or injection-related reactions	13 (2.0)	4 (1.2)
Cancer	31 (4.7)	14 (4.3)

PEARL Studies
conclusion

- **Monthly administration of peginesatide was as effective as administration of darbepoetin every 2 weeks in increasing and maintaining hemoglobin levels in patients with chronic kidney disease who were not receiving dialysis.**

- **There was an increase in cardiovascular events and deaths with peginesatide that was unexpected and remains unexplained, underscoring the need for additional data to clarify the benefit–risk profile of peginesatide in this patient population.**

The NEW ENGLAND JOURNAL of MEDICINE

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Peginesatide in Patients with Anemia Undergoing Hemodialysis

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ABSTRACT

BACKGROUND

Peginesatide, a synthetic peptide-based erythropoiesis-stimulating agent (ESA), is a potential therapy for anemia in patients with advanced chronic kidney disease.

METHODS

We conducted two randomized, controlled, open-label studies (EMERALD 1 and EMERALD 2) involving patients undergoing hemodialysis. Cardiovascular safety was evaluated by analysis of an adjudicated composite safety end point — death from any cause, stroke, myocardial infarction, or serious adverse events of congestive heart failure, unstable angina, or arrhythmia — with the use of pooled data from the two EMERALD studies and two studies involving patients not undergoing dialysis. In the EMERALD studies, 1608 patients received peginesatide once monthly or continued to receive epoetin one to three times a week, with the doses adjusted as necessary to maintain a hemoglobin level between 10.0 and 12.0 g per deciliter for 52 weeks or more. The primary efficacy end point was the mean change from the baseline hemoglobin level to the mean level during the evaluation period; noninferiority was established if the lower limit of the two-sided 95% confidence interval was −1.0 g per deciliter or higher in the comparison of peginesatide with epoetin. The aim of evaluating the composite safety end point in the pooled cohort was to exclude a hazard ratio with peginesatide relative to the comparator ESA of more than 1.3.

RESULTS

In an analysis involving 693 patients from EMERALD 1 and 725 from EMERALD 2, peginesatide was noninferior to epoetin in maintaining hemoglobin levels (mean between-group difference, −0.15 g per deciliter; 95% confidence interval [CI], −0.30 to −0.01 in EMERALD 1; and 0.10 g per deciliter; 95% CI, −0.05 to 0.26 in EMERALD 2). The hazard ratio for the composite safety end point was 1.06 (95% CI, 0.89 to 1.26) with peginesatide relative to the comparator ESA in the four pooled studies (2591 patients) and 0.95 (95% CI, 0.77 to 1.17) in the EMERALD studies. The proportions of patients with adverse and serious adverse events were similar in the treatment groups in the EMERALD studies. The cardiovascular safety of peginesatide was similar to that of the comparator ESA in the pooled cohort.

CONCLUSIONS

Peginesatide, administered monthly, was as effective as epoetin, administered one to three times per week, in maintaining hemoglobin levels in patients undergoing hemodialysis. (Funded by Affymax and Takeda Pharmaceutical; ClinicalTrials.gov numbers, NCT00597753 [EMERALD 1], NCT00597584 [EMERALD 2], NCT00598273 [PEARL 1], and NCT00598442 [PEARL 2].)

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*Investigators and committee members for the Efficacy and Safety of Peginesatide for the Maintenance Treatment of Anemia in Patients with Chronic Renal Failure Who Were Receiving Hemodialysis and Were Previously Treated with Epoetin (EMERALD) studies are listed [illegible] able at NEJM.org.

N Engl J Med 2013;368:307-19.
DOI: 10.1056/NEJMoa1203165

EMRALD

(Efficacy and Safety of Peginesatide for the Maintenance Treatment of Anemia in Patients with Chronic Renal Failure Who Were Receiving Hemodialysis).

EMRALD Study

- **Study Oversight**
- Phase III ,randomized, active-treatment–controlled, open label, noninferiority studies in the United States (EMERALD 1 and EMERALD 2) and in Europe (EMERALD 2).
- Patients 18 years of age or older with chronic kidney disease were eligible if they had been undergoing hemodialysis for at least 3 months .
- **Study Procedures**
- Each study included a 6-week screening period, a 28-week initial dose-adjustment period, an 8-week evaluation period, and a longer-term follow-up period (≥16 additional weeks).
- Eligible patients were randomly assigned, in a 2:1 ratio, to receive peginesatide once every 4 weeks or to continue to receive epoetin one to three times a week.

EMRALD Study

The primary efficacy end point

Hemoglobin concentration was maintained within the target range during the evaluation period

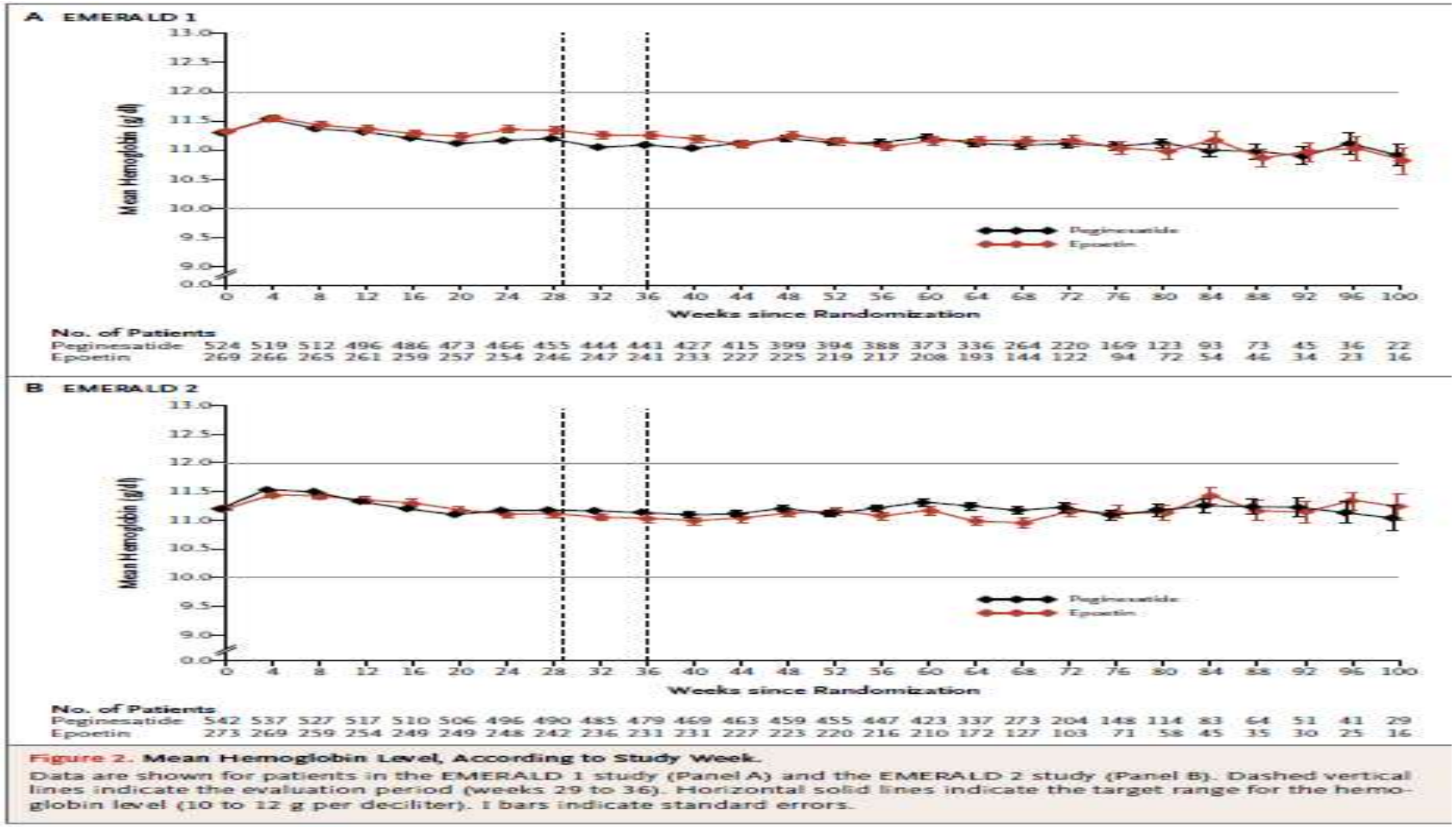

Figure 2. **Mean Hemoglobin Level, According to Study Week.**
Data are shown for patients in the EMERALD 1 study (Panel A) and the EMERALD 2 study (Panel B). Dashed vertical lines indicate the evaluation period (weeks 29 to 36). Horizontal solid lines indicate the target range for the hemoglobin level (10 to 12 g per deciliter). I bars indicate standard errors.

EMRALD Study

- **Adverse Events**
- Adverse (including serious adverse) events in the EMERALD studies were similar in the peginesatide and epoetin groups and were consistent with expected adverse events in patients undergoing hemodialysis.
- The peginesatide group had higher rates of coronary artery disease (in the EMERALD 1 study) and arrhythmia (in the EMERALD 2 study).

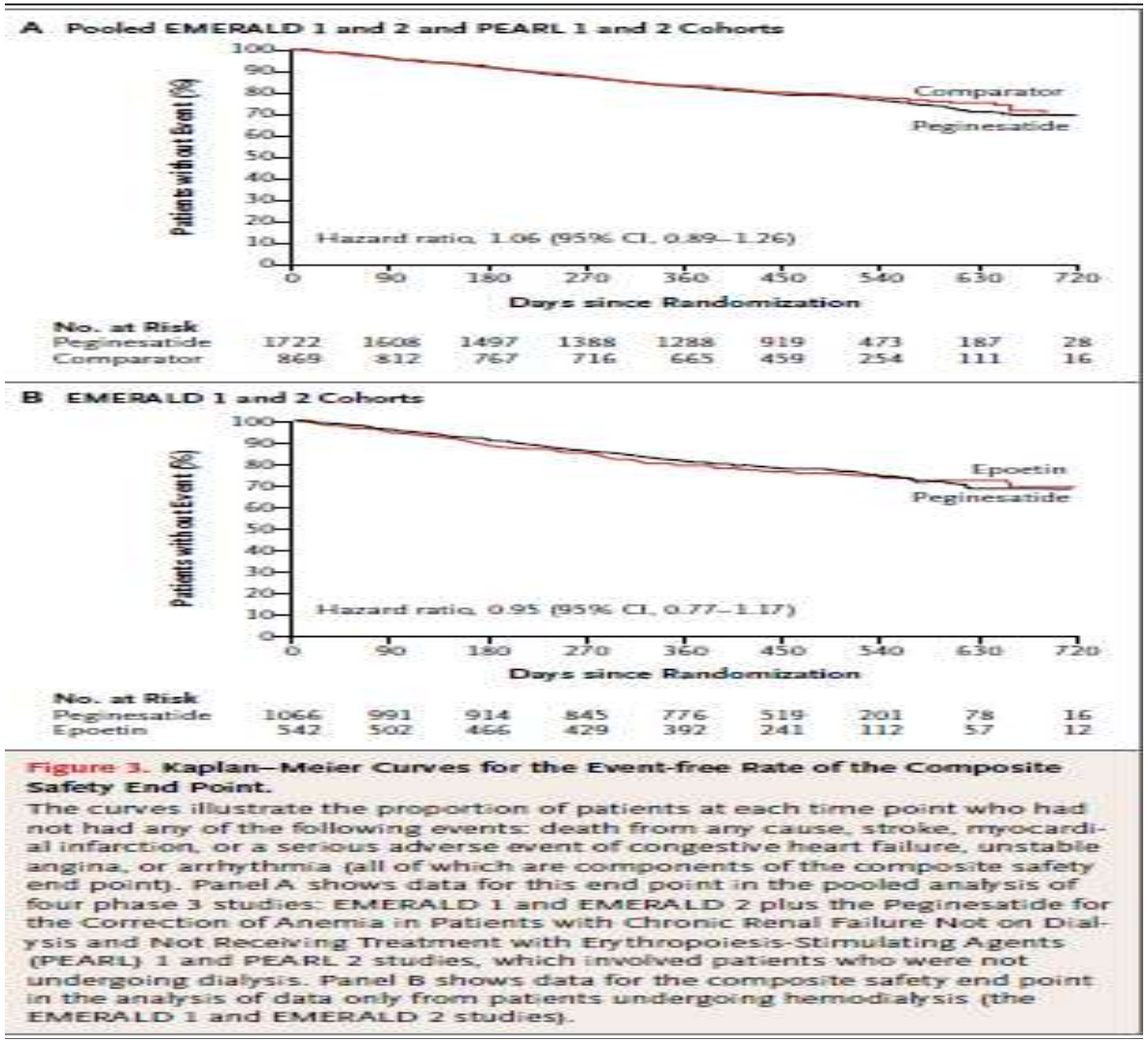

Figure 3. Kaplan–Meier Curves for the Event-free Rate of the Composite Safety End Point.
The curves illustrate the proportion of patients at each time point who had not had any of the following events: death from any cause, stroke, myocardial infarction, or a serious adverse event of congestive heart failure, unstable angina, or arrhythmia (all of which are components of the composite safety end point). Panel A shows data for this end point in the pooled analysis of four phase 3 studies: EMERALD 1 and EMERALD 2 plus the Peginesatide for the Correction of Anemia in Patients with Chronic Renal Failure Not on Dialysis and Not Receiving Treatment with Erythropoiesis-Stimulating Agents (PEARL) 1 and PEARL 2 studies, which involved patients who were not undergoing dialysis. Panel B shows data for the composite safety end point in the analysis of data only from patients undergoing hemodialysis (the EMERALD 1 and EMERALD 2 studies).

EMRALD Study conclusion

Peginesatide, administered once a month, was similar to epoetin, administered one to three times a week, for the treatment of anemia in patients receiving hemodialysis.

Peginesatide
Phase 3 Clinical Trials

Study	Description	Sample Size (region)	Outcomes
PEARL 1	Correction study: peginesatide vs darbepoetin alfa in nondialysis patients (SC)	~330 vs 165 (US)	Efficacy of peginesatide noninferior to darbepoetin; increased HR for composite safety end point at 1.32 for peginesatide vs darbepoetin alfa
PEARL 2	Correction study: peginesatide vs darbepoetin alfa in nondialysis patients (SC)	~330 vs 165 (US and Europe)	
EMERALD 1	Maintenance study: peginesatide vs epoetin alfa in dialysis patients (IV)	~540 vs 270 (US)	Efficacy and safety of peginesatide noninferior to epoetin
EMERALD 2	Maintenance study: peginesatide vs epoetin alfa or beta in dialysis patients (IV/SC)	~540 vs 270 (US and Europe)	

Abbreviations: EMERALD, Hematide Injection for Anemia in Chronic Hemodialysis Patients; HR, hazard ratio; IV, intravenous; PEARL, Safety and Efficacy of Hematide for the Correction of Anemia in Patients With Chronic Renal Failure; SC, subcutaneous; US, United States.

Modified Erythropoietin Molecules Under Development

- Attempts have been made to fuse EPO with unrelated peptides

Human Chorionic gonadotropin Beta (beta HCG)

- Increase the *in vivo* potency and circulatory half-life of the molecule.
- This approach has been used to create an Fc fusion protein (Syntonix Pharmaceuticals, Inc) that canbe administered by aerosol inhalation.

Dumont JA, et al., J Aerosol Med, 2005;18:294–303.

Albumin

- **Three kinds of albumin–EPO fusion proteins (IALE, AD2LE and AD1LE)**
- **A non-glycosylated denatured EPO was obtained from *Escherichia coli* and then refolded and pegylated.**

Joung CH, et al., Protein Expr Purif, 2009;68:137–45.

Wang, et al., Int J Pharm, 2010;386:156–64.

- **All these EPO-modified proteins raise some concerns about immunogenicity.**

International Journal of Pharmaceutics 386 (2010) 156–164

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Efficient preparation and PEGylation of recombinant human non-glycosylated erythropoietin expressed as inclusion body in *E. coli*

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[c] Beijing University of Chemical Technology, Beijing 100029, China

Protein Expression and Purification 68 (2009) 137–145

Contents lists available at ScienceDirect

Protein Expression and Purification

journal homepage: www.elsevier.com/locate/yprep

Production and characterization of long-acting recombinant human albumin–EPO fusion protein expressed in CHO cell

Chan-Hi Joung, Ju-Yeop Shin, Jae-Kyung Koo, Jin J. Lim, Jin-Sang Wang, Song-Jae Lee, Hyun-Kwang Tan, Sang-Lin Kim, Sang-Min Lim*

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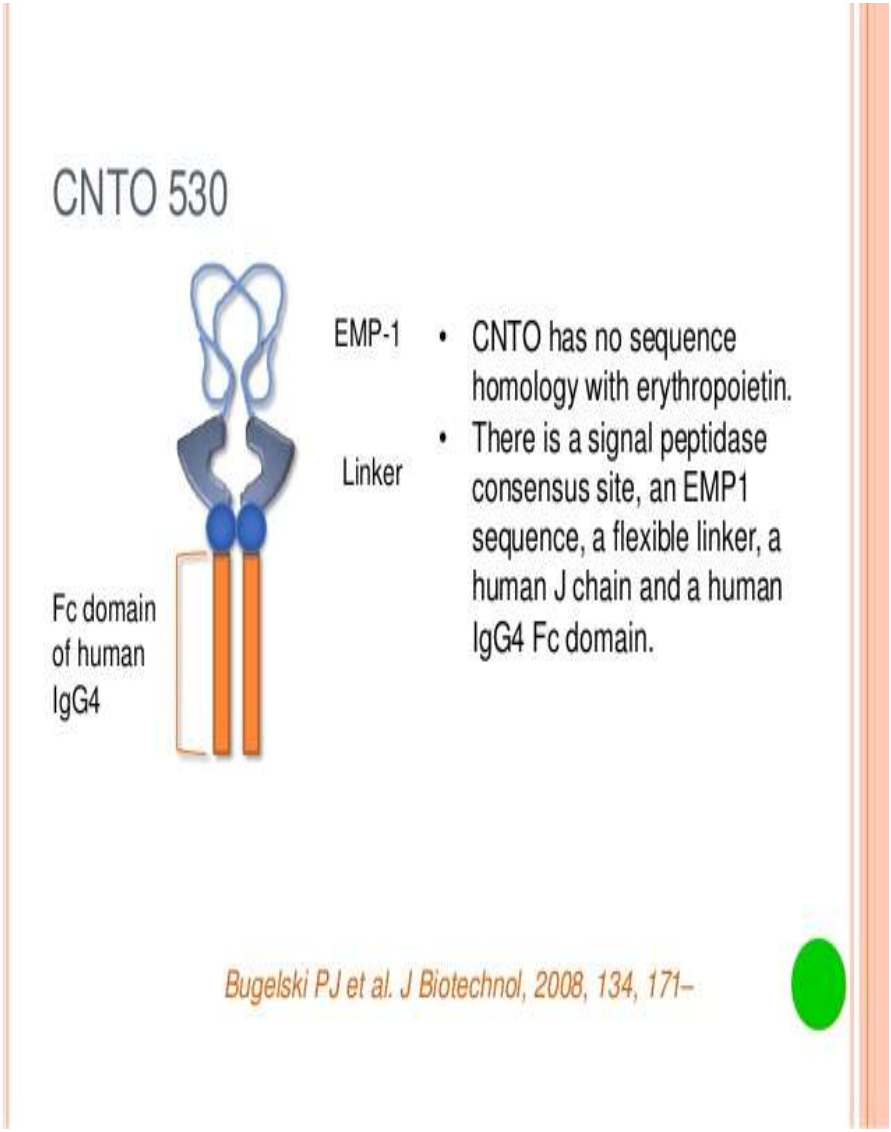
Non-Epo derived EPO receptor agonist

- **Two other non-erythropoietin-derived EPO-receptor agonists**
- **CNTO 530 :**
- **Two sequences of a 20-amino acid peptide with weak EPO-like bioactivity (EMP1) were coupled with a human immunoglobulin (Ig) G4 Fc.**
- **Selectively binds the EPO-receptor.**
- **In animal studies, it is a more potent stimulator of erythropoiesis than epoetin-alpha or darbepoetin alpha.**

Sathyanarayana P, et al.,, *Blood,2009*

- **CNTO 528:**
- **A similar molecule, CNTO 528, has undergone phase I clinical development.**
- **Single intravenous administration stimulated the production of reticulocytes, red blood cells and haemoglobin in 24 healthy volunteers.**
- **Of the ESAs developed to date, CNTO 528 has the longest half-life (four to seven days).**

Bouman-Thio E,et al. ., A phase I, *J Clin Pharmacol ,2008*

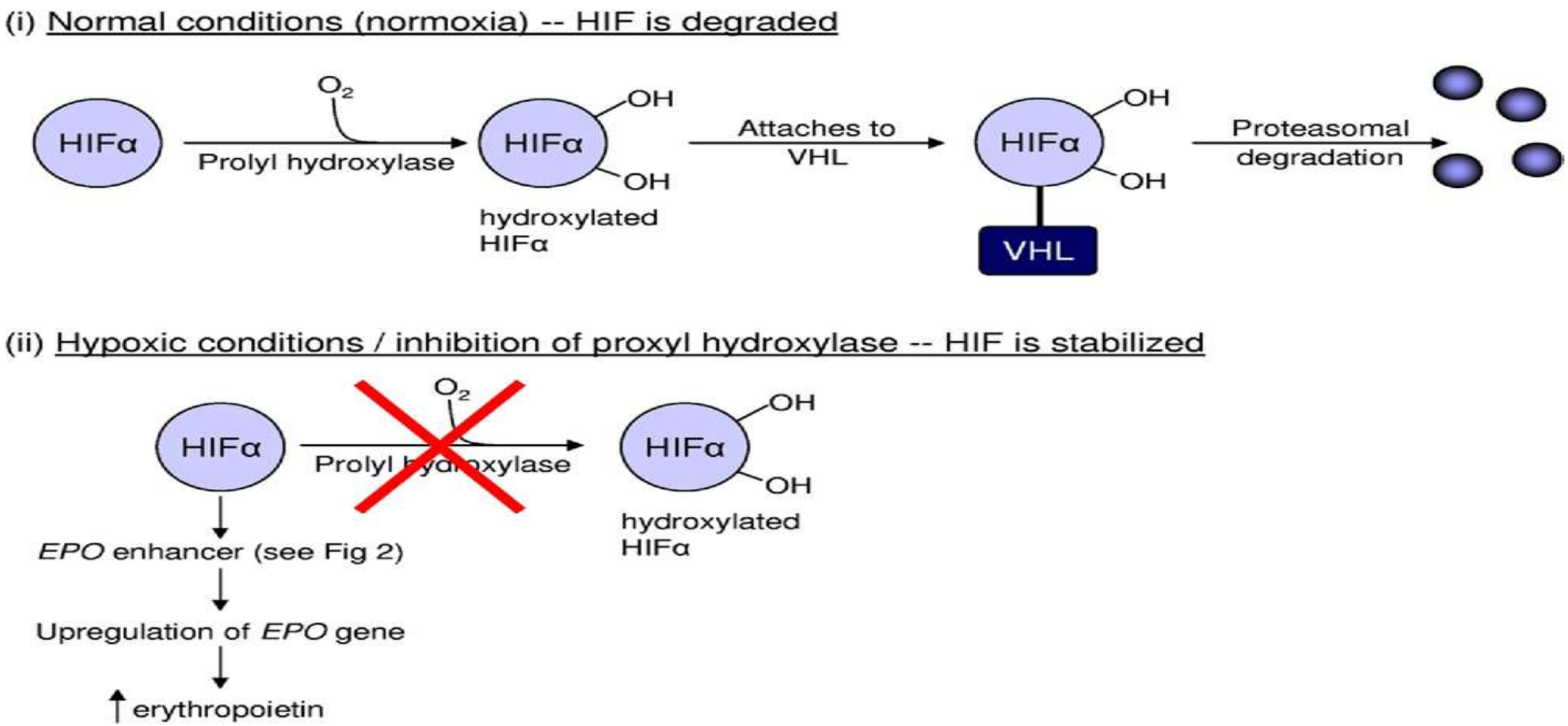


2-HIF STABILIZATION
3-GATA 2 INHIBITOR

HIF STABILIZATION

Regulation of *EPO* (erythropoietin) gene expression

Regulation of hypoxia inducible factor (HIF) activity.
Abbreviations: EPO, erythropoietin; VHL, von Hippel Lindau protein.



HIF STABILIZATION

- FG-2216
- FG-4592
- GSK1278863
- BAY85-3934e
- AKB-6548

HIF STABILIZATION

FG-2216

Preconditional Activation of Hypoxia-Inducible Factors Ameliorates Ischemic Acute Renal Failure

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Activation of hypoxia-inducible transcription factor (HIF) has been identified as an important mechanism of cellular adaptation to low oxygen. Normoxic degradation of HIF is mediated by oxygen-dependent hydroxylation of specific prolyl residues of the regulative α-subunits by HIF prolyl hydroxylases (PHD). It was hypothesized that inhibition of HIF degradation by either hypoxia or pharmacologic inhibition of PHD would confer protection against subsequent ischemic injury. For testing this hypothesis ischemic acute renal failure was induced in rats by 40 min of clamping of the left renal artery after right-sided nephrectomy. Before surgery, pretreatment with either carbon monoxide, leading to tissue hypoxia, or the novel PHD inhibitor FG-4487 was applied. No toxic effects of FG-4487 were observed. Both pretreatments strongly induced the accumulation of HIF-1α and HIF-2α in tubular and peritubular cells, respectively, as well as HIF target gene expression. The course of subsequent ischemic injury was significantly ameliorated by both strategies of preconditioning, as evident from a significant improvement of serum creatinine and serum urea after 24 and 72 h. Furthermore, tissue injury and apoptosis were less severe, which were quantified by application of a standardized histologic scoring system in a blinded manner. In conclusion, the data provide proof of principle that preconditional activation of the HIF system protects against ischemic injury. Inhibiting the activity of HIF hydroxylases therefore seems to have considerable clinical perspectives.

J Am Soc Nephrol 17: 1970–1978, 2006. doi: 10.1681/ASN.2005121302

FG-2216 Corrects Anemia and Improves Iron Utilization in a Rat Model of Anemia of Chronic Disease: Comparison to Darbepoetin

Ingrid Langsetmo, Blake Nichols, Todd Seeley, Bob Stephenson, Steve Klaus, Al Lin, David Liu
FibroGen, South San Francisco, CA

[Show | Hide Abstract]

Anemia of Chronic Disease (ACD) is characterized by a blunted erythropoietin response, decreased iron utilization and impaired response of the bone marrow. Patients with impaired iron utilization are hyporesponsive to rHuEPO therapies. FG-2216 stimulates eEPO production, improves iron absorption and utilization and overcomes the inflammatory suppression of erythropoiesis. The objective of this study was to compare FG-2216 to darbepoetin in a rat model of ACD. Administration of peptidoglycan-polysaccharide polymers (PGPS) to female Lewis rats causes inflammation and disrupted iron utilization leading to a prolonged microcytic hypochromic anemia. Four weeks prior to treatment, rats were injected with PGPS to induce arthritis and anemia (Hb < 10 g/dL). Normal and anemic animals were treated with vehicle, FG-2216, darbepoetin or IV iron. After four weeks of treatment, FG-2216 and darbepoetin produced dramatic and equivalent increases in both Hb and Hct in normal animals. However, in PGPS challenged animals, FG-2216 increased Hb and Hct to levels comparable to normal controls, while darbepoetin had no effect. Intravenous iron had no effect in either normal or anemic animals. In addition, FG-2216 improved the microcytosis and increased MCH, demonstrating improved iron utilization. Darbepoetin did not improve MCV or MCH in anemic animals and reduced MCV and MCH in the normal group. Transcript analysis of duodenum and liver demonstrated increased expression of iron transport proteins and decreased expression of hepcidin (a hormone involved in negative regulation of circulating iron levels) in the FG-2216 treated group compared to all other groups. FG-2216 reversed the anemia associated with PGPS-induced arthritis in rats, while a functionally equivalent dose of darbepoetin was unable to stimulate erythropoiesis. By coordinating iron availability with erythropoietic stimulation, FG-2216 may be better able to overcome inflammatory suppression of erythropoiesis and thereby provide an important benefit to patients needing treatment for erythropoietin-resistant anemia and ACD.

HIF STABILIZATION
FG-2216

- **In a Phase II clinical trial, one patient developed fatal hepatic necrosis after receiving a HIF stabilizer .**

- **In addition to this death, other patients developed abnormal liver function tests, prompting the FDA to suspend further clinical trial.**

Leyland-Jones B. Lancet Oncol 2003;4(8):459-60

Nephrol Dial Transplant (2015) 30: 1665–1673
doi: 10.1093/ndt/gfv302
Advance Access publication 3 August 2015

ndt
Nephrology Dialysis Transplantati

FASTTRACK *Original Article*

Randomized placebo-controlled dose-ranging and pharmacodynamics study of roxadustat (FG-4592) to treat anemia in nondialysis-dependent chronic kidney disease (NDD-CKD) patients

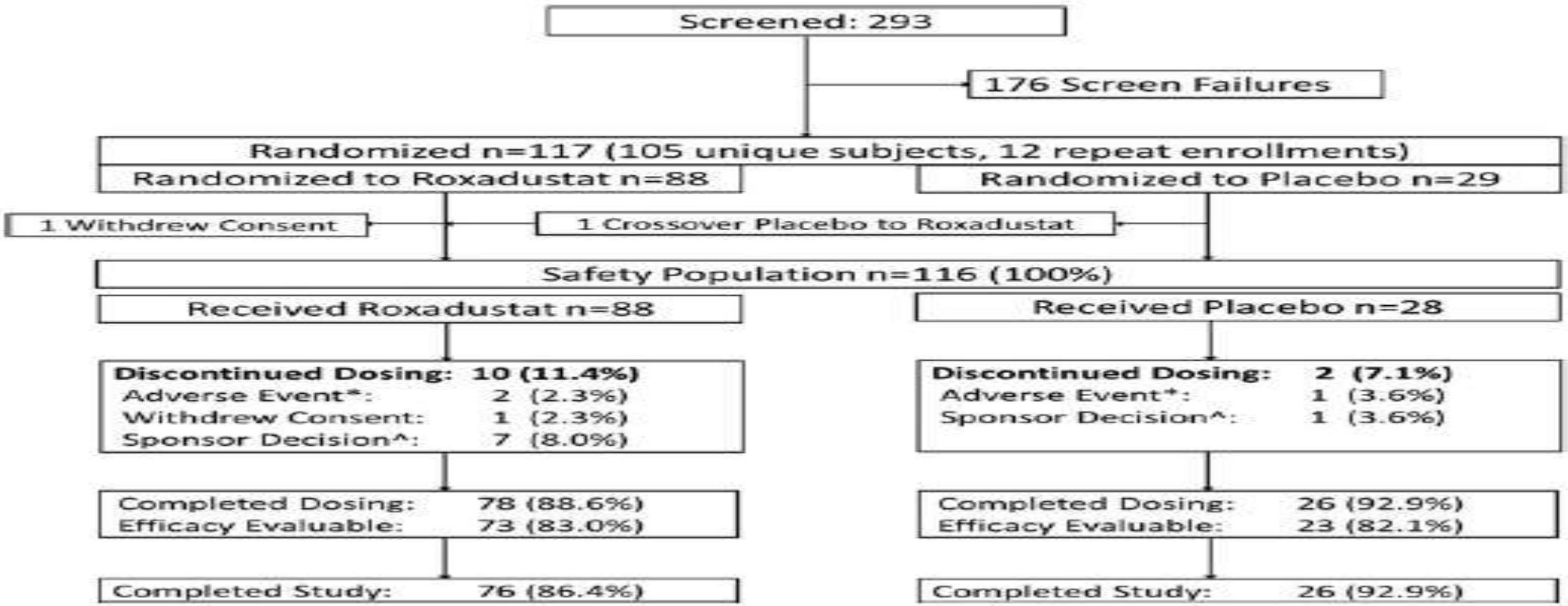
Anatole Besarab[1], Robert Provenzano[2], Joachim Hertel[3], Raja Zabaneh[4], Stephen J. Klaus[1], Tyson Lee[1], Robert Leong[1], Stefan Hemmerich[1], Kin-Hung Peony Yu[1] and Thomas B. Neff[1]

[1]FibroGen, Inc., San Francisco, CA, USA, [2]St Clair Specialty Physicians, Detroit, MI, USA, [3]Kidney Care Associates, LLC, Augusta, GA, USA and [4]Northwest Louisiana Nephrology, Shreveport, LA, USA

Randomized placebo-controlled dose-ranging and pharmacodynamics study of roxadustat (FG-4592) to treat anemia in nondialysis-dependent chronic kidney disease (NDD-CKD) patients

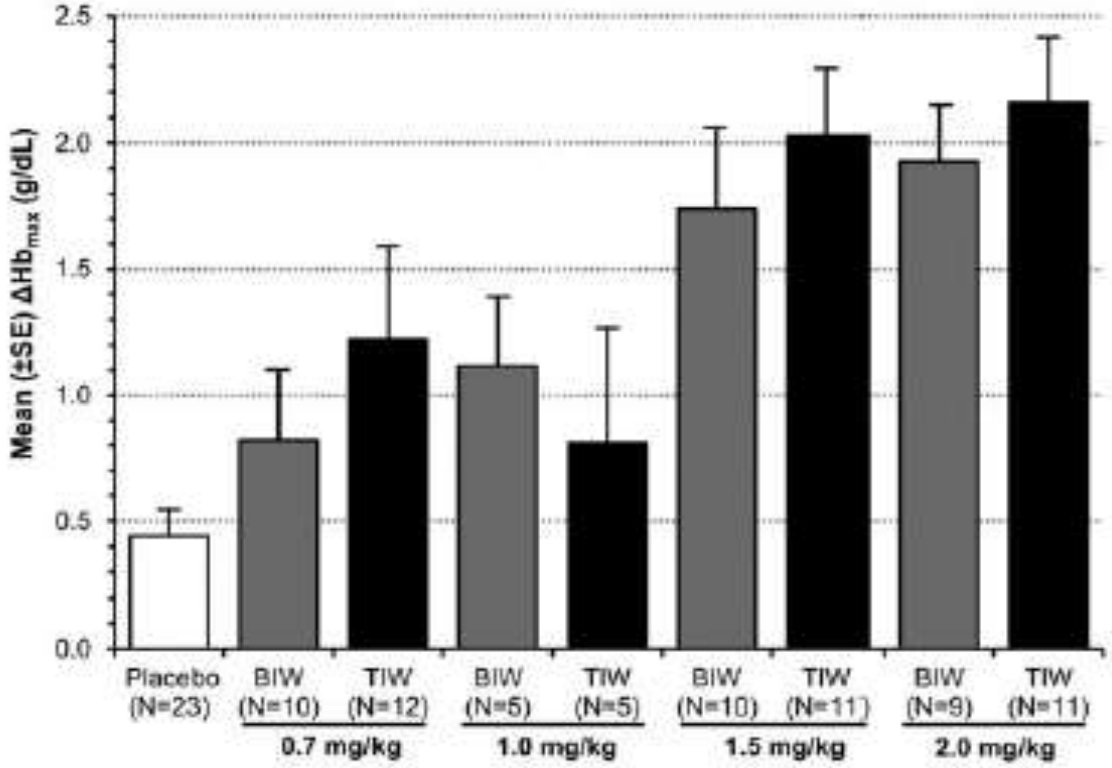
- **Roxadustat, also known as FG-4592, is a first in class, potent hypoxia-inducible factor prolyl hydroxylase inhibitor (HIFPHI).**
- **The first Phase 2 clinical trial of roxadustat in anemic NDD-CKD patients.**
- **Oral roxadustat administered BIW or TIW in NDD-CKD patients**

Randomized placebo-controlled dose-ranging and pharmacodynamics study of roxadustat (FG-4592) to treat anemia in nondialysis-dependent chronic kidney disease (NDD-CKD) patients

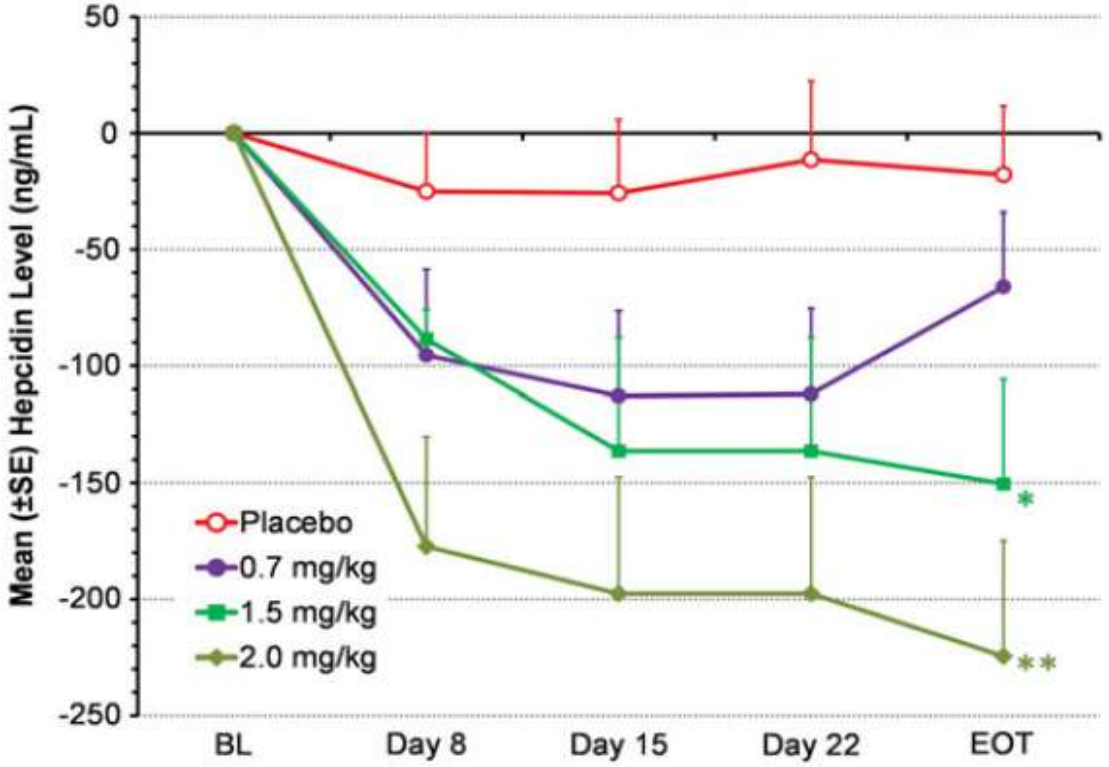


Randomized placebo-controlled dose-ranging and pharmacodynamics study of roxadustat (FG-4592) to treat anemia in nondialysis-dependent chronic kidney disease (NDD-CKD) patients

Hb response



Mean change from BL in serum hepcidin



Randomized placebo-controlled dose-ranging and pharmacodynamics study of roxadustat (FG-4592) to treat anemia in nondialysis-dependent chronic kidney disease (NDD-CKD) patients

- **In summary, oral roxadustat administered BIW or TIW in NDD-CKD patients increased Hb in the absence of IV iron supplementation.**

- **The balance of benefits and risks with roxadustat is being evaluated in ongoing large, controlled trials in both nondialysis and dialysis populations.**

Advantages of HIF stabilization therapy.

- 1- The strategy of stimulating endogenous erythropoietin production is interesting not only for its lack of need for exogenous ESA therapy.
- 2-These agents are orally active and thus there is potential for a noninjectable anemia therapy in the future.
- 3-These molecules are able to modulate a number of other genes involved in erythropoiesis (eg, the erythropoietin receptor, transferrin, transferrin receptor, ferroportin, and divalent metal transporter in addition to the *EPO* gene).

Haase VH. Am J Physiol Renal Physiol. 2010;299:F1-F13.

Possible disadvantages

- **FG-2216 In a phase 2 clinical trial, a patient developed fatal hepatic necrosis, and this was related temporally to administration of the HIF stabilizer.**

Astellas Pharma Inc. Adverse event of FG-2216 for the treatment of anemia. Media Release May 07, 2007.

- **The potential ability of these compounds to upregulate vascular endothelial growth factor (VEGF), which may have the adverse consequence of causing tumor growth and proliferative diabetic retinopathy .**

Toffoli S, Roegiers A, Feron O, et al. *Angiogenesis*. 2009;12:47-67

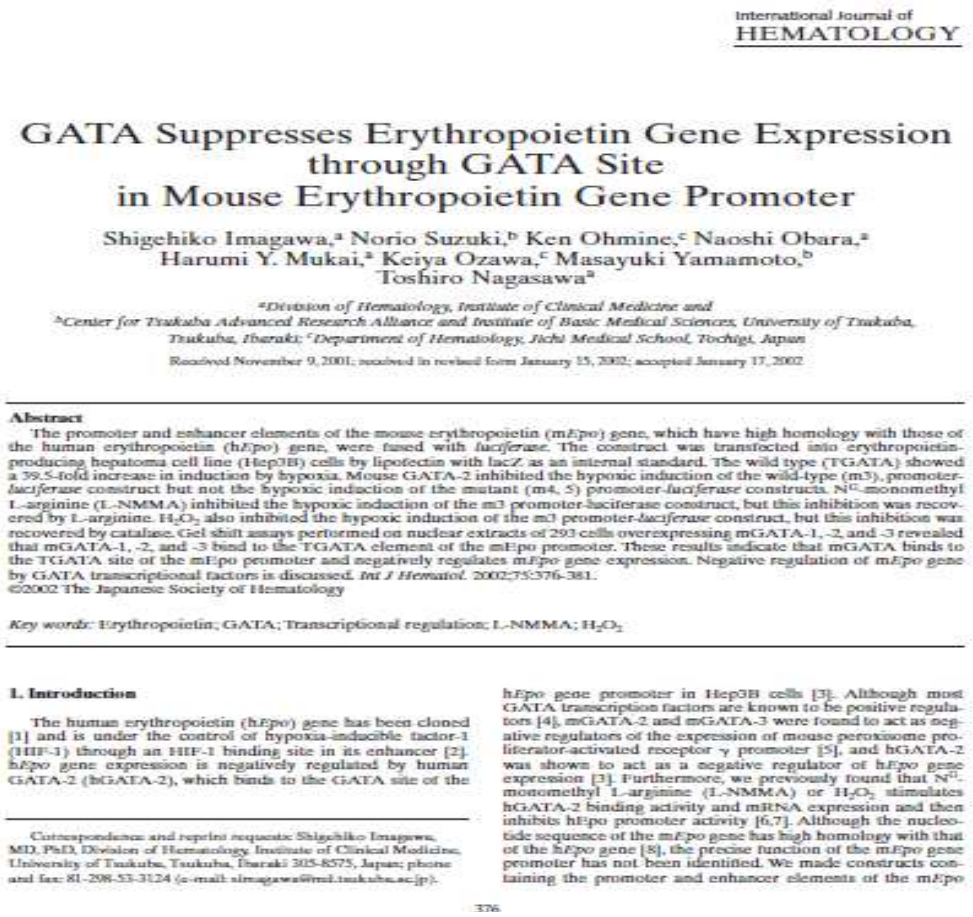
3- GATA-2 INHIBITORS

GATA-2 INHIBITORS

- K-7174
- K-11706

GATA-2 INHIBITORS

- **Imagawa et al studied the effects of K-7174 in both a human hepatoma cell line (Hep3B cells in 1% oxygen) and an animal model of anemia .**
- **GATA specific inhibitor potentiated erythropoietin protein production and *EPO* promoter activity that previously had been suppressed with IL-1, TNF- (tumor necrosis factor).**
- **Similarly, in the animal model, K-7174 was able to reverse the decrease in hemoglobin levels and reticulocyte counts induced by intraperitoneal injection of IL-1 or TNF- in mice.**



International Journal of
HEMATOLOGY

GATA Suppresses Erythropoietin Gene Expression through GATA Site in Mouse Erythropoietin Gene Promoter

Shigehiko Imagawa,[a] Norio Suzuki,[b] Ken Ohmine,[c] Naoshi Obara,[a] Harumi Y. Mukai,[a] Keiya Ozawa,[c] Masayuki Yamamoto,[b] Toshiro Nagasawa[a]

[a]*Division of Hematology, Institute of Clinical Medicine and [b]Center for Tsukuba Advanced Research Alliance and Institute of Basic Medical Sciences, University of Tsukuba, Tsukuba, Ibaraki; [c]Department of Hematology, Jichi Medical School, Tochigi, Japan*

Received November 9, 2001; received in revised form January 15, 2002; accepted January 17, 2002

Abstract

The promoter and enhancer elements of the mouse erythropoietin (m*Epo*) gene, which have high homology with those of the human erythropoietin (h*Epo*) gene, were fused with *luciferase*. The construct was transfected into erythropoietin-producing hepatoma cell line (Hep3B) cells by lipofectin with lacZ as an internal standard. The wild type (TGATA) showed a 39.5-fold increase in induction by hypoxia. Mouse GATA-2 inhibited the hypoxic induction of the wild-type (m3), promoter-*luciferase* construct but not the hypoxic induction of the mutant (m4, 5) promoter-*luciferase* constructs. N^G-monomethyl L-arginine (L-NMMA) inhibited the hypoxic induction of the m3 promoter-luciferase construct, but this inhibition was recovered by L-arginine. H_2O_2 also inhibited the hypoxic induction of the m3 promoter-*luciferase* construct, but this inhibition was recovered by catalase. Gel shift assays performed on nuclear extracts of 293 cells overexpressing mGATA-1, -2, and -3 revealed that mGATA-1, -2, and -3 bind to the TGATA element of the m*Epo* promoter. These results indicate that mGATA binds to the TGATA site of the m*Epo* promoter and negatively regulates m*Epo* gene expression. Negative regulation of m*Epo* gene by GATA transcriptional factors is discussed. *Int J Hematol.* 2002;75:376-381.

Key words: Erythropoietin; GATA; Transcriptional regulation; L-NMMA; H_2O_2

1. Introduction

The human erythropoietin (h*Epo*) gene has been cloned [1] and is under the control of hypoxia-inducible factor-1 (HIF-1) through an HIF-1 binding site in its enhancer [2]. h*Epo* gene expression is negatively regulated by human GATA-2 (hGATA-2), which binds to the GATA site of the h*Epo* gene promoter in Hep3B cells [3]. Although most GATA transcription factors are known to be positive regulators [4], mGATA-2 and mGATA-3 were found to act as negative regulators of the expression of mouse peroxisome proliferator-activated receptor γ promoter [5], and hGATA-2 was shown to act as a negative regulator of h*Epo* gene expression [3]. Furthermore, we previously found that N^G-monomethyl L-arginine (L-NMMA) or H_2O_2 stimulates hGATA-2 binding activity and mRNA expression and then inhibits hEpo promoter activity [6,7]. Although the nucleotide sequence of the m*Epo* gene has high homology with that of the h*Epo* gene [8], the precise function of the m*Epo* gene promoter has not been identified. We made constructs containing the promoter and enhancer elements of the m*Epo*

Correspondence and reprint requests: Shigehiko Imagawa, MD, PhD, Division of Hematology, Institute of Clinical Medicine, University of Tsukuba, Tsukuba, Ibaraki 305-8575, Japan; phone and fax: 81-298-53-3124 (e-mail: simagawa@md.tsukuba.ac.jp).

GATA-2 INHIBITORS

Oral administration of K-11706 inhibits GATA binding activity, enhances hypoxia-inducible factor 1 binding activity, and restores indicators in an in vivo mouse model of anemia of chronic disease

Yoko Nakano, Shigehiko Imagawa, Ken Matsumoto, Christian Stockmann, Naoshi Obara, Norio Suzuki, Takeshi Doi, Tatsuhiko Kodama, Satoru Takahashi, Toshiro Nagasawa, and Masayuki Yamamoto

Erythropoietin (Epo) gene expression is under the control of hypoxia-inducible factor 1 (HIF-1), and is negatively regulated by GATA. Interleukin 1β (IL-1β) and tumor necrosis factor α (TNF-α), which increase the binding activity of GATA and inhibit Epo promoter activity, are increased in patients with anemia of chronic disease (ACD). We previously demonstrated the ability of K-7174 (a GATA-specific inhibitor), when injected intraperitoneally, to improve Epo production that had been inhibited by IL-1β or TNF-α treatment. In the present study, we examined the ability of both K-11706, which inhibits GATA and enhances HIF-1 binding activity, and K-13144, which has no effect on GATA or HIF-1 binding activity, to improve Epo production following inhibition by IL-1β or TNF-α in Hep3B cells in vitro and in an in vivo mouse assay. Oral administration of K-11706 reversed the decreases in hemoglobin and serum Epo concentrations, reticulocyte counts, and numbers of erythroid colony-forming units (CFU-Es) induced by IL-1β or TNF-α. These results raise the possibility of using orally administered K-11706 for treating patients with ACD. (Blood. 2004; 104:4300-4307)

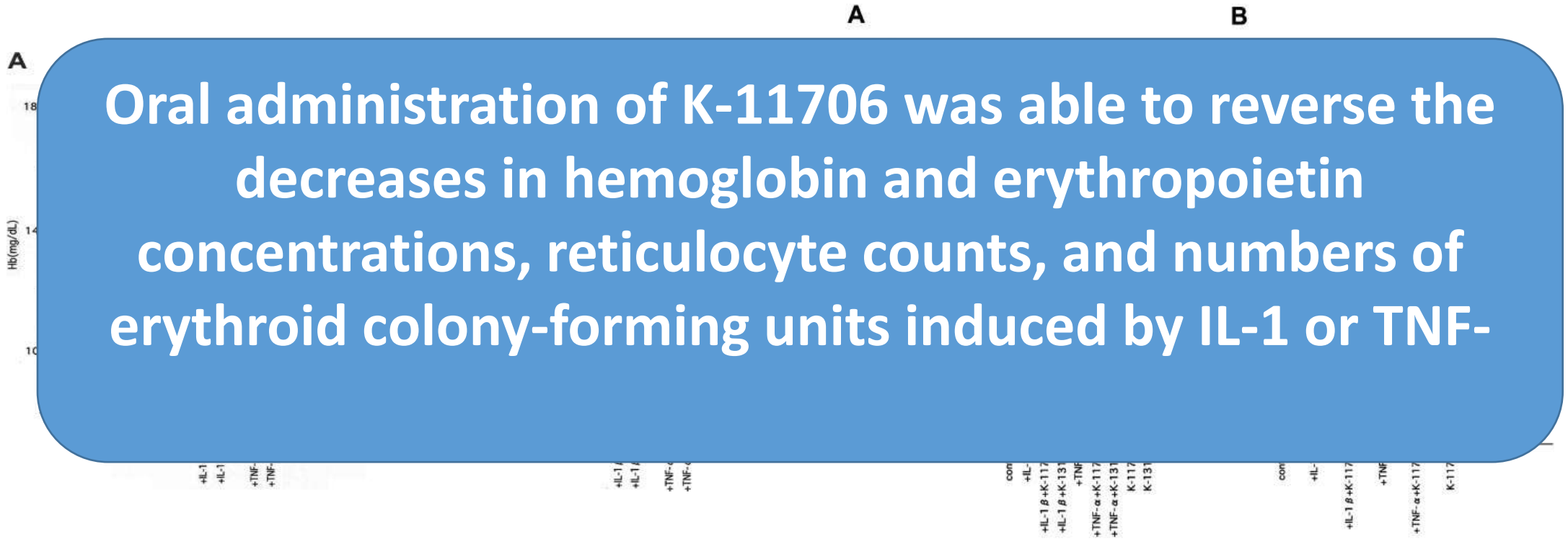
Introduction

- The same group of Japanese scientists then investigated whether another molecule with GATA-inhibiting properties (K-11706) could improve erythropoietin production in the same cellular and animal models.

GATA-2 INHIBITORS

Effects of K-11706 or K-13144 on hemoglobin and erythropoietin.

Effects of K-11706 or K-13144 on reticulocyte counts and numbers of CFU-Es.



Oral administration of K-11706 was able to reverse the decreases in hemoglobin and erythropoietin concentrations, reticulocyte counts, and numbers of erythroid colony-forming units induced by IL-1 or TNF-

GATA-2 INHIBITORS

- In comparing the 2 molecules, K-11706 was found to evoke greater hypoxic induction compared with K-7174, possibly through stimulation of HIF-1 binding activity in addition to GATA inhibition.
- Results from both these studies suggest a potential role for an orally administered GATA inhibitor in the treatment of anemia.

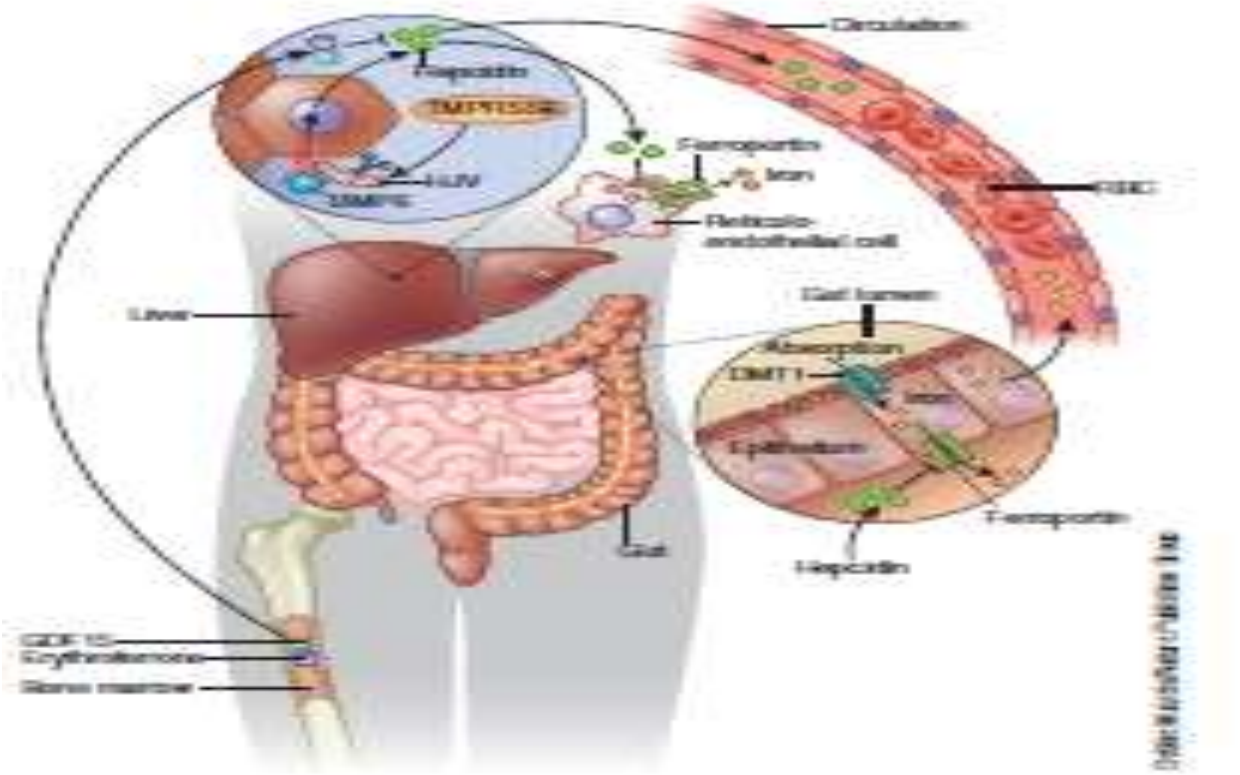
GATA-2 INHIBITORS

- There is concern that GATA inhibition will promote activation of other genes in addition to erythropoietin.
- GATA inhibition can promote activation of other genes in addition to EPO and lead to adverse effects related to insulin control, tumor promotion, and diabetic retinopathy.

4-Hepcidin Modulation

Hepcidin Modulation

Regulation of iron homeostasis



- **Hepcidin is a small defensin-like peptide produced largely by the liver macrophage and adipocyte.**
- **Secreted hepcidin (green circles) binds the iron transporter(ferroportin) and stimulates its degradation, resulting in decreased intestinal iron (orange circles) absorption and iron accumulation in reticuloendothelial cells.**

Hepcidin Modulation

• Upregulated

- Inflammation(interleukin 6 (IL-6) BMP-6 (bone morphogenetic protein 6) and iron overload.
- Uremia, as a chronic inflammatory state, also upregulates hepcidin, and in particular, dialysis patients have much higher serum hepcidin levels than healthy individuals.

• Downregulated

- by anemia, hypoxia, and iron deficiency.

Hepcidin Modulation

- **1- An RNA-based hepcidin antagonist, consisting of a 44-nucleotide L-RNA oligonucleotide, has been linked to improving anemia in cynomolgus monkeys.**

- **2- Another strategy could be to inhibit the production of hepcidin. This could be achieved by using antisense oligonucleotides or silencing messenger RNA transcribed from the hepcidin gene (*HAMP*).**

Firth HV, Hurst JA. Oxford desk reference: clinical genetics. 1st edition. Oxford University Press; 2005

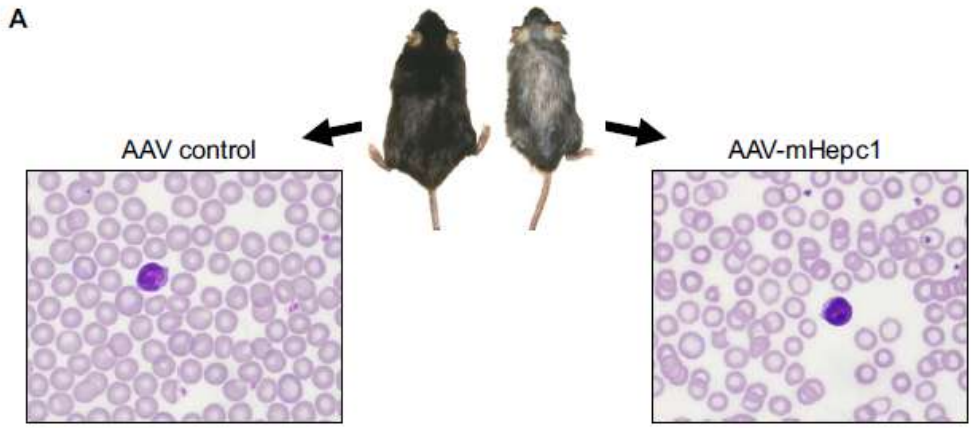
Hepcidin Modulation

- A monoclonal antibody against hepcidin has been shown to improve anemia in an inflammatory mouse model.

Antihepcidin antibody treatment modulates iron metabolism and is effective in a mouse model of inflammation-induced anemia

Barbra J. Sasu,[1] Keegan S. Cooke,[1] Tara L. Arvedson,[1] Cherylene Plewa,[2] Aaron R. Ellison,[2] Jackie Sheng,[2] Aaron Winters,[2] Todd Juan,[2] Hongyan Li,[3] C. Glenn Begley,[1] and Graham Molineux[1]

Departments of [1]Hematology/Oncology, [2]Protein Sciences, and [3]Pharmacokinetics and Drug Metabolism, Amgen Inc, Thousand Oaks, CA



BLOOD, 29 APRIL 2010 • VOLUME 115, NUMBER 17

Hepcidin Modulation

- None of the strategies to suppress hepcidin production or antagonize this peptide have been subjected to Human clinical trials.
- A theoretical concern could be that inhibition of hepcidin might :
- 1- exacerbate the risk of infections, given its endogenous antimicrobial properties.
- 1- Stabilization of HIF in some studies enhances tumor growth, stabilization of HIF in some studies enhances tumor growth
- 3- Interruption of BMP (particularly BMP-6) may result in calcification of tissues (including peritoneum) .
- 4- Interruption of the binding of hepcidin to ferroportin may enhance iron absorption and mobilization .
- A possible solution to this problem could entail the suppression of hepcidin to appropriate levels without complete inhibition of hepcidin production.

Sun CC,. Am J Hematol 2012

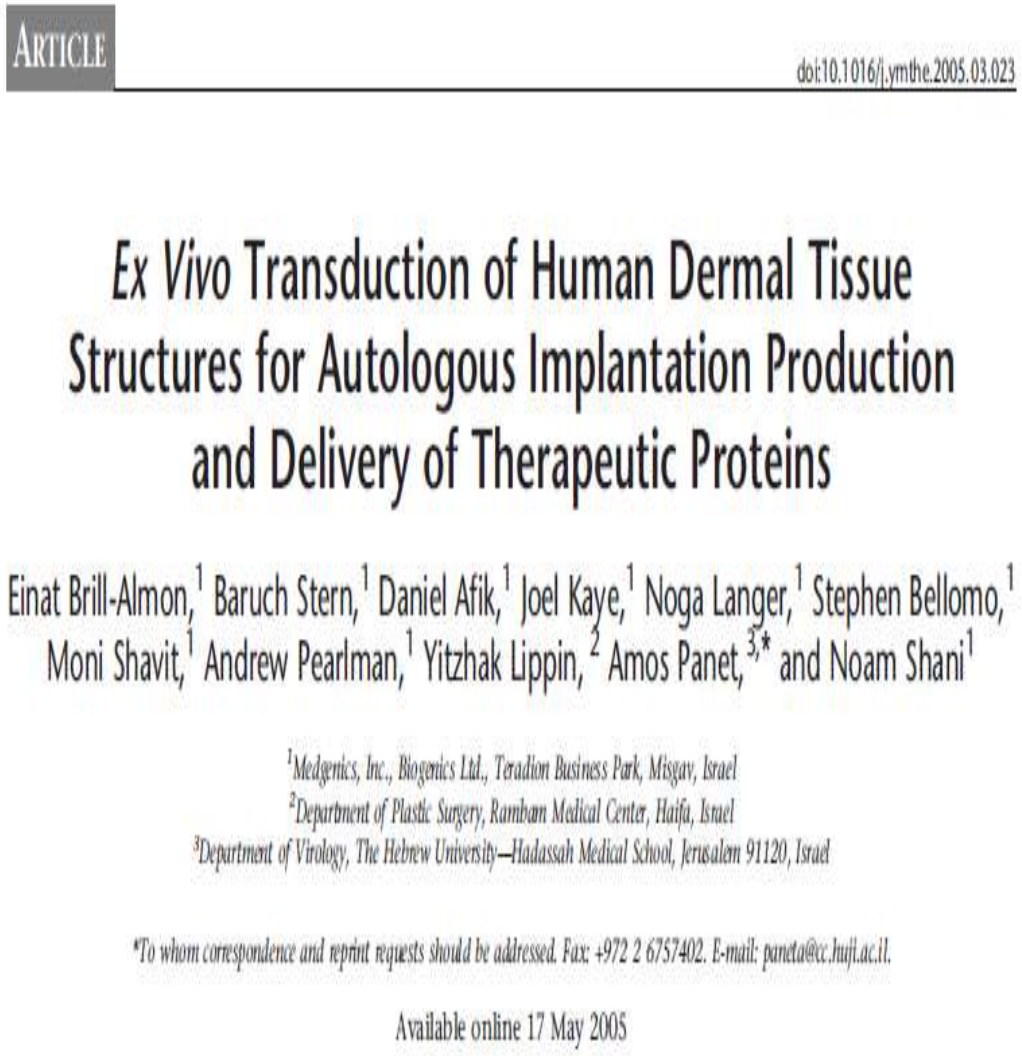
5- ERYTHROPOIETIN GENE THERAPY

ERYTHROPOIETIN GENE THERAPY

- **Several years ago, a group of Israeli scientists developed a functional delivery system for the *EPO* gene using skin cells.**

Brill-Almon E, et al.. Mol Ther. 2005;12: 274-282.

- **The early experiments were conducted in mice.**
- **The basic methodology involved extracting a microbiopsy specimen of dermal cells, harvesting them, and transducing them with the *EPO* gene (using an adenovirus vector), and then reimplanting the preparation back into the mice.**
- **The mice responded by producing increased levels of erythropoietin, and this was associated with an increase in hematocrit.**



ARTICLE

doi:10.1016/j.ymthe.2005.03.023

Ex Vivo Transduction of Human Dermal Tissue Structures for Autologous Implantation Production and Delivery of Therapeutic Proteins

Einat Brill-Almon,[1] Baruch Stern,[1] Daniel Afik,[1] Joel Kaye,[1] Noga Langer,[1] Stephen Bellomo,[1] Moni Shavit,[1] Andrew Pearlman,[1] Yitzhak Lippin,[2] Amos Panet,[3,*] and Noam Shani[1]

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[2]*Department of Plastic Surgery, Rambam Medical Center, Haifa, Israel*
[3]*Department of Virology, The Hebrew University—Hadassah Medical School, Jerusalem 91120, Israel*

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Available online 17 May 2005

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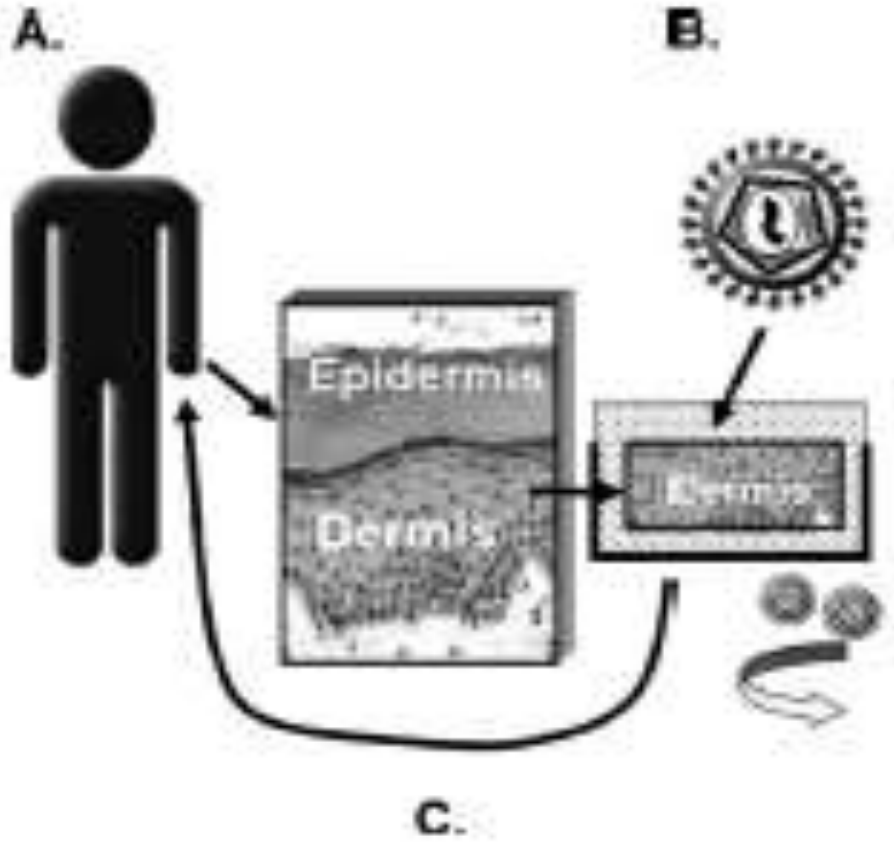
[3]*Department of Virology, The Hebrew University—Hadassah Medical School, Jerusalem 91120, Israel*

*To whom correspondence and reprint requests should be addressed. Fax: +972 2 6757402. E-mail: panetat@cc.huji.ac.il.

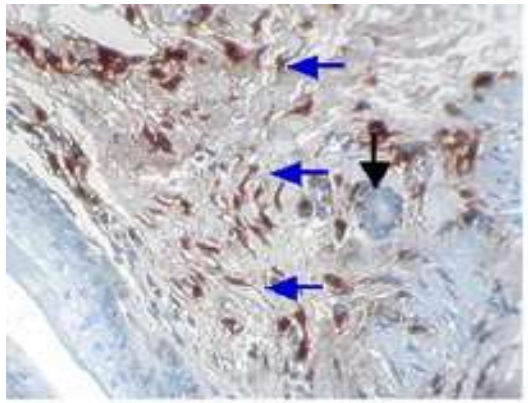
Available online 17 May 2005

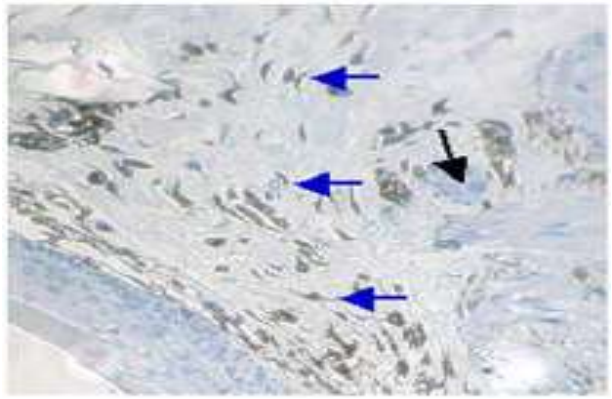
- **Scheme of the microdermis technology:**



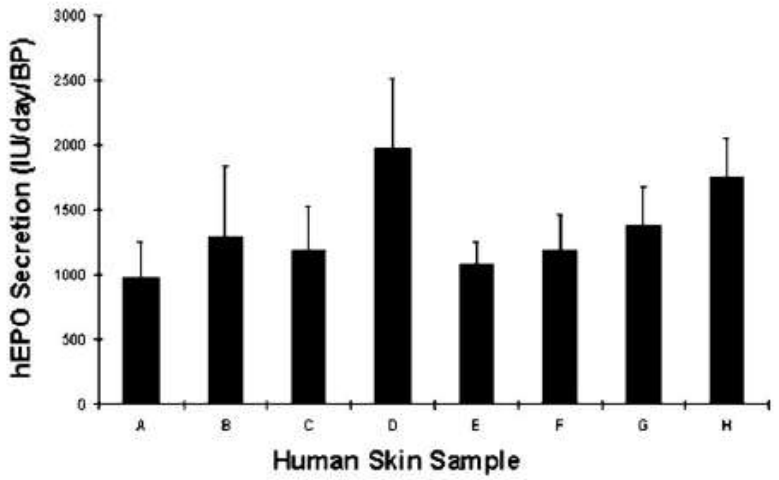
- **(A) A miniature dermal structure is removed from the patient's skin using a specialized device.**
- **(B) Viral vectors transfer the gene into dermal cells .**
- **Following the transduction procedure the desired protein is secreted into the culture medium and quantified by ELISA.**
- **(C) The measured protein secretion rate is used to estimate the number of autologous microdermises to be implanted to provide the desired therapeutic protein level in the patient.**
- **D) Following sterility and viability tests the microdermis is reimplanted subcutaneously using an injection-like procedure. There, it integrates as normal tissue, delivering the therapeutic protein to the patient.**

ERYTHROPOIETIN GENE THERAPY





Many of the hEPO-producing cells are fibroblasts (blue arrows), which are spread throughout the dermis (blood vessels are noted by black arrows)



Therapeutic levels of hEPO are produced by fibroblasts within the dermis.

ERYTHROPOIETIN GENE THERAPY

- **A small group of patients with CKD in Israel have taken part in a proof-of-concept phase 1-2 clinical trial of this delivery system for the EPO gene.**
- **All patients showed increased erythropoietin production, with most showing sustained elevation of hemoglobin levels (the primary end point) in the target range of 10-12 g/dL for 6-12 months without receiving additional erythropoietin injections.**
- **One patient maintained hemoglobin levels in the normal range for more than 18 months without erythropoietin injections.**

- Medgenics press release April 27, 2010. Medgenics granted approval for extension of anaemia trial. http://www.medgenics.com/downloads/Announcement-MOH_270410. pdf. Accessed October15, 2011

Vitamin E -coated polysulfone membrane

Vitamin E - Coated Membranes

- **Oxidative stress may have an independent negative role on anaemia and ESA responsiveness; anecdotal data suggest that oral vitamin E supplementation may improve ESA responsiveness.**

- **Given that blood–membrane interaction plays a key role in generating oxidative stress, direct free-radical scavenging at the membrane site has been proposed.**

- **Some studies tested the role of vitamin E-coated membranes on ESA responsiveness.**

Vitamin E Coated Membrane

ORIGINAL ARTICLE

JNEPHROL 2013; 26 (3): 556-563

DOI: 10.5301/jn.5000195

Vitamin E–coated polysulfone membrane improved red blood cell antioxidant status in hemodialysis patients

Anne-Sophie Bargnoux [1,2], Jean-Paul Cristol [1,2], Isabelle Jaussent [3], Lotfi Chalabi [4], Pierre Bories [5], Jean-Jacques Dion [6], Patrick Henri [7], Martine Delage [1], Anne-Marie Dupuy [1], Stéphanie Badiou [1,2], Bernard Canaud [2,4,8,9], Marion Morena [1,2,9]

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[2] Mixed Research Unit UMR 204 Nutripass, University of Montpellier 1, Montpellier - France
[3] National Institute of Health and Medical Research (INSERM), U1061, Montpellier - France
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[5] Department of Nephrology, Toulouse University Hospital, Toulouse - France
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[8] Department of Nephrology, Dialysis and Intensive Care, Montpellier University Hospital, Montpellier - France
[9] Dialysis Research and Training Institute, Montpellier University Hospital, Montpellier - France

Vitamin E Coated Membrane

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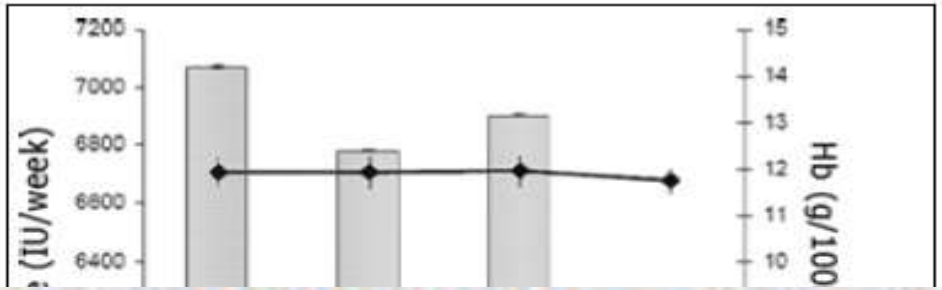
[1] Biochemistry Laboratory, Montpellier University Hospital, Montpellier - France
[2] Mixed Research Unit UMR 204 Nutripass, University of Montpellier 1, Montpellier - France
[3] National Institute of Health and Medical Research (INSERM), U1061, Montpellier - France
[4] Association pour l'Installation à Domicile des Epurations

Effect of short term use of vitamin E–coated polysulfone membrane on predialysis hemoglobin (Hb) levels and weekly (EPO) dose (columns) from hemodialysis .



Conclusions: Use of the vitE-PS membrane during a short period improves erythrocyte antioxidant defense mechanisms and seems to lead to a reduction in EPO requirements in HD patients.

Vitamin E Coated Membrane

Nephrol Dial Transplant (2014) 29: 649–656
doi: 10.1093/ndt/gft481
Advance Access publication 28 November 2013

ORIGINAL ARTICLE

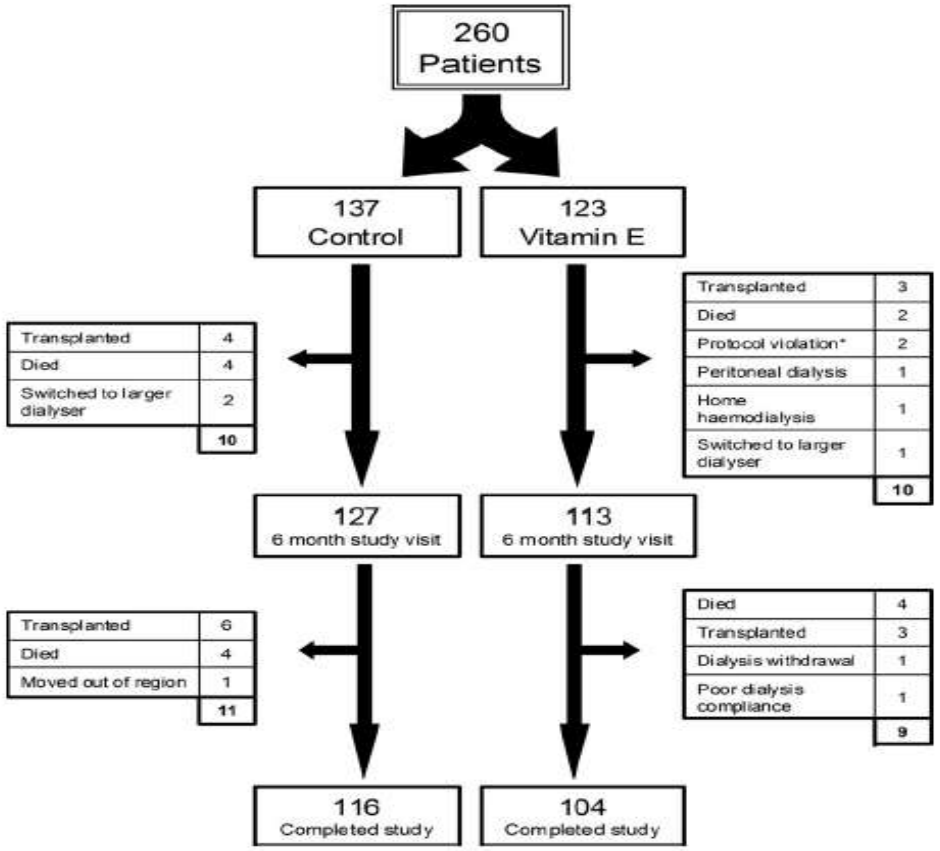
A randomized controlled trial evaluating the erythropoiesis stimulating agent sparing potential of a vitamin E-bonded polysulfone dialysis membrane

Simon W. Lines[1,2], Angela M. Carter[2], Emma J. Dunn[1], Elizabeth J. Lindley[1], James E. Tattersall[1] and Mark J. Wright[1]

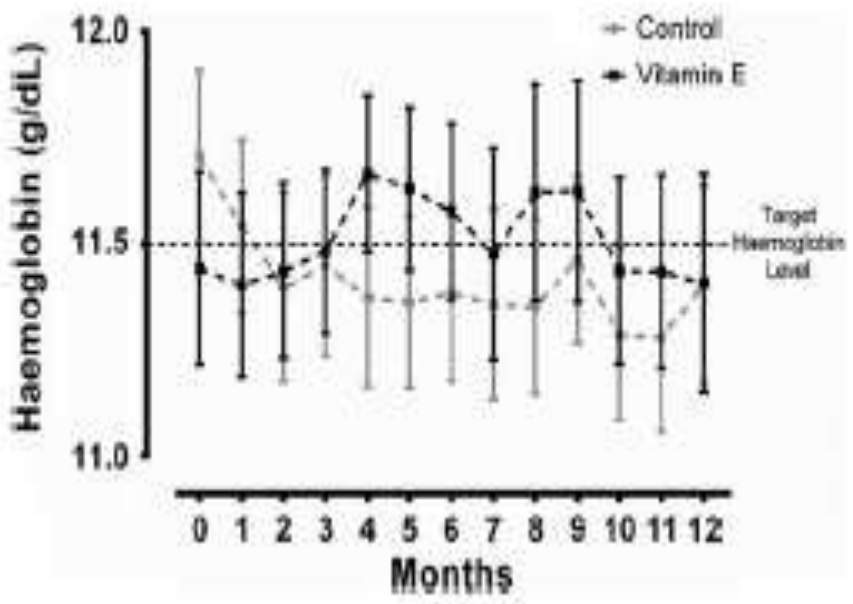
[1]Department of Nephrology, St. James's University Hospital, Leeds, UK and [2]Division of Cardiovascular and Diabetes Research, University of Leeds, Leeds, UK

Correspondence and offprint requests to: Simon Lines; E-mail: simonlines@doctors.net.uk

Vitamin E Coated Membrane

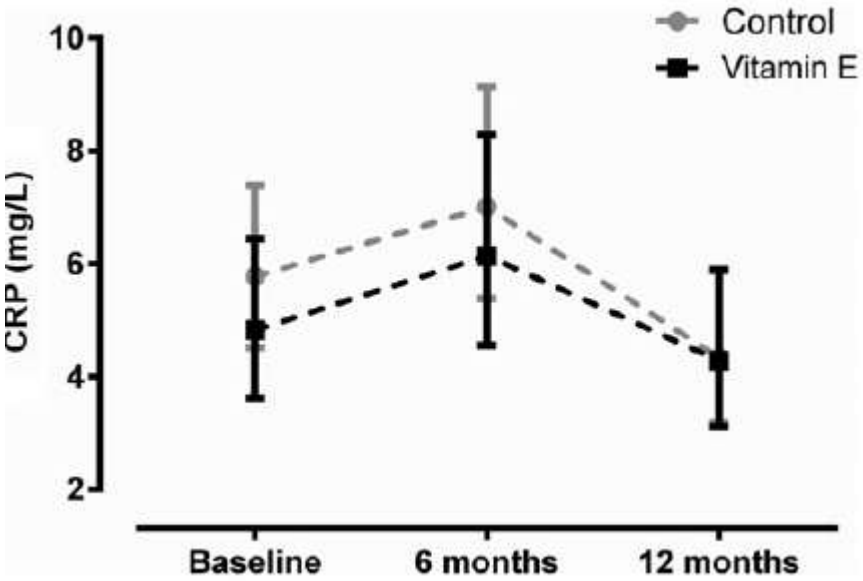


Mean monthly haemoglobin levels for haemodialysis patients randomized to vitamin E or control membranes.

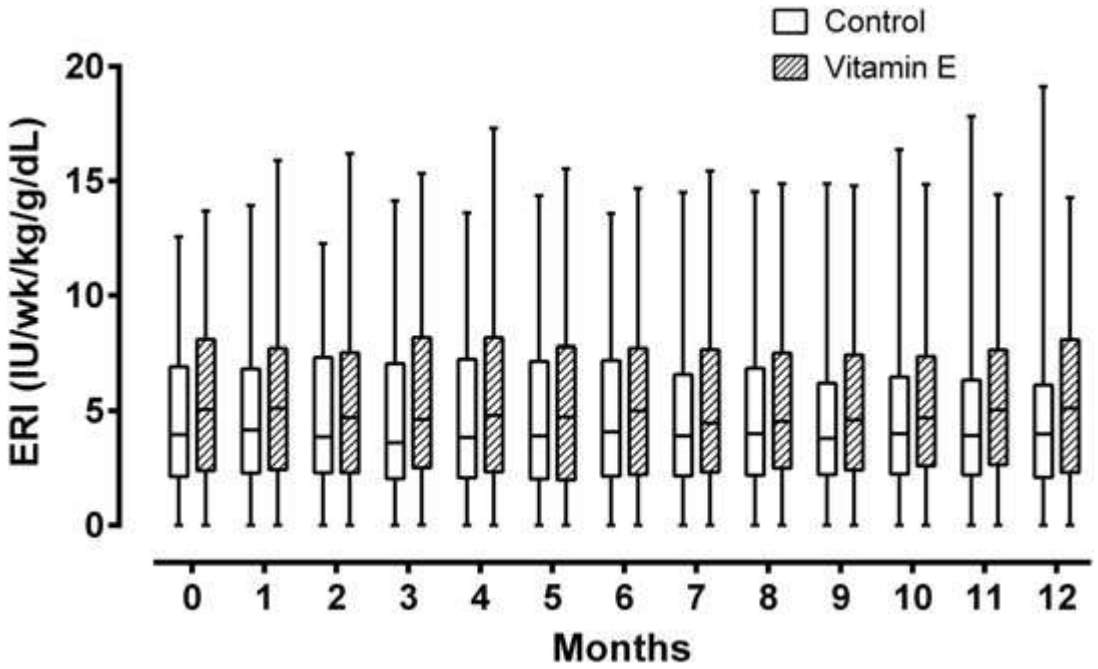


Vitamin E Coated Membrane

CRP levels for haemodialysis patients randomized to vitamin E or control membranes, followed up at 6 and 12 months.

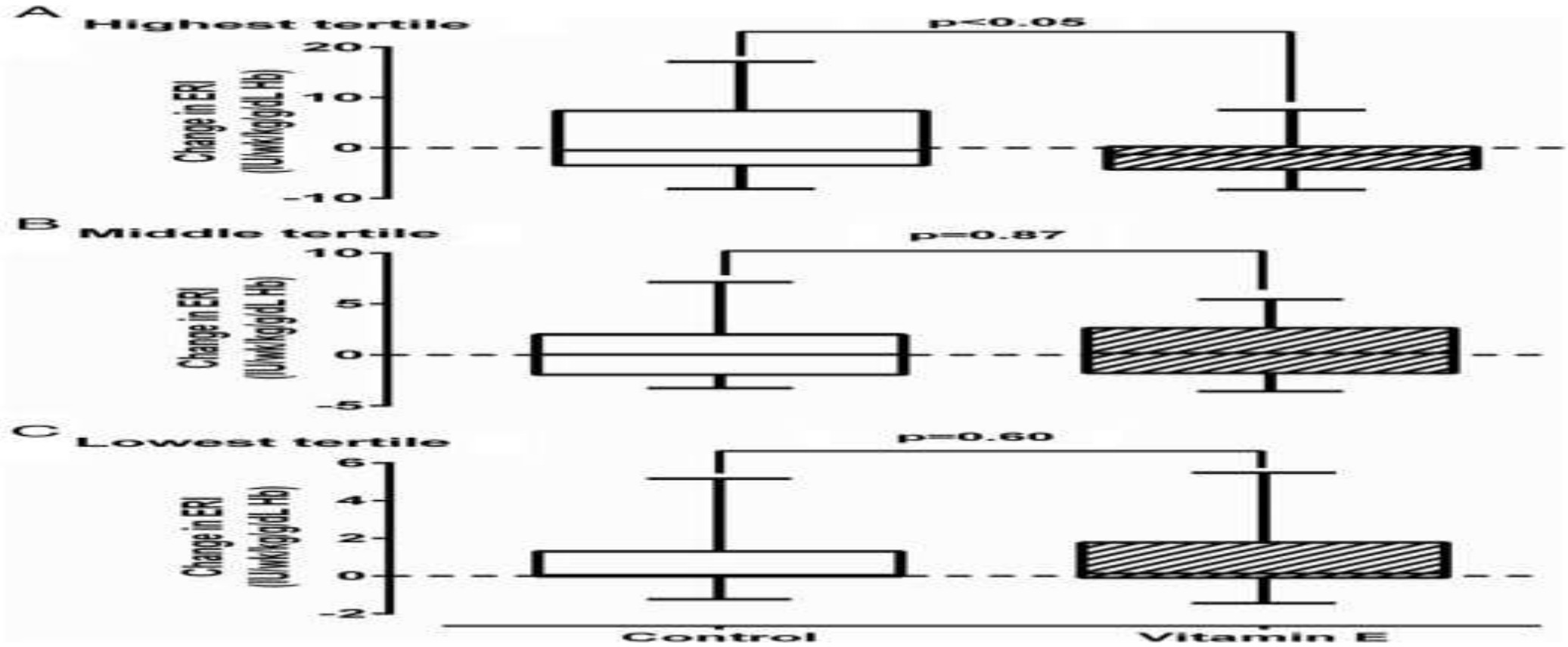


Median monthly ERIs for haemodialysis patients randomized to vitamin E or control membranes



Vitamin E Coated Membrane

Comparison of 12-month change in ERI between haemodialysis patients randomized to vitamin E and control membranes stratified by of baseline ERI



Conclusion

Conclusion

- **ESAs have been used as a standard treatment option to alleviate symptoms of anemia since 1989.**
- **The lessons we learned from recombinant human erythropoietin therapy were that although we proved early that this agent could increase hemoglobin levels, it took us nearly 20 years to realize the limitations of this therapy and the potential for harm if used too aggressively.**

- **Despite new drugs, our ‘good old friend’ erythropoietin stimulating agents are our everyday life in nephrology practice.**

Conclusion

- Recently, newer strategies for correcting anemia have been explored, some of which remain in the laboratory while others are translating across into clinical trials.
- Newer ESA derivatives are being developed to be safer, less expensive, and more convenient to administer.
- The use of these newer therapeutic options shows great promise in improving the risk-benefit ratio of ESAs .
- Before these new agents are adopted into clinical practice more research must be conducted in order to prevent or at least minimize unexpected and severe toxicities.

Thank You